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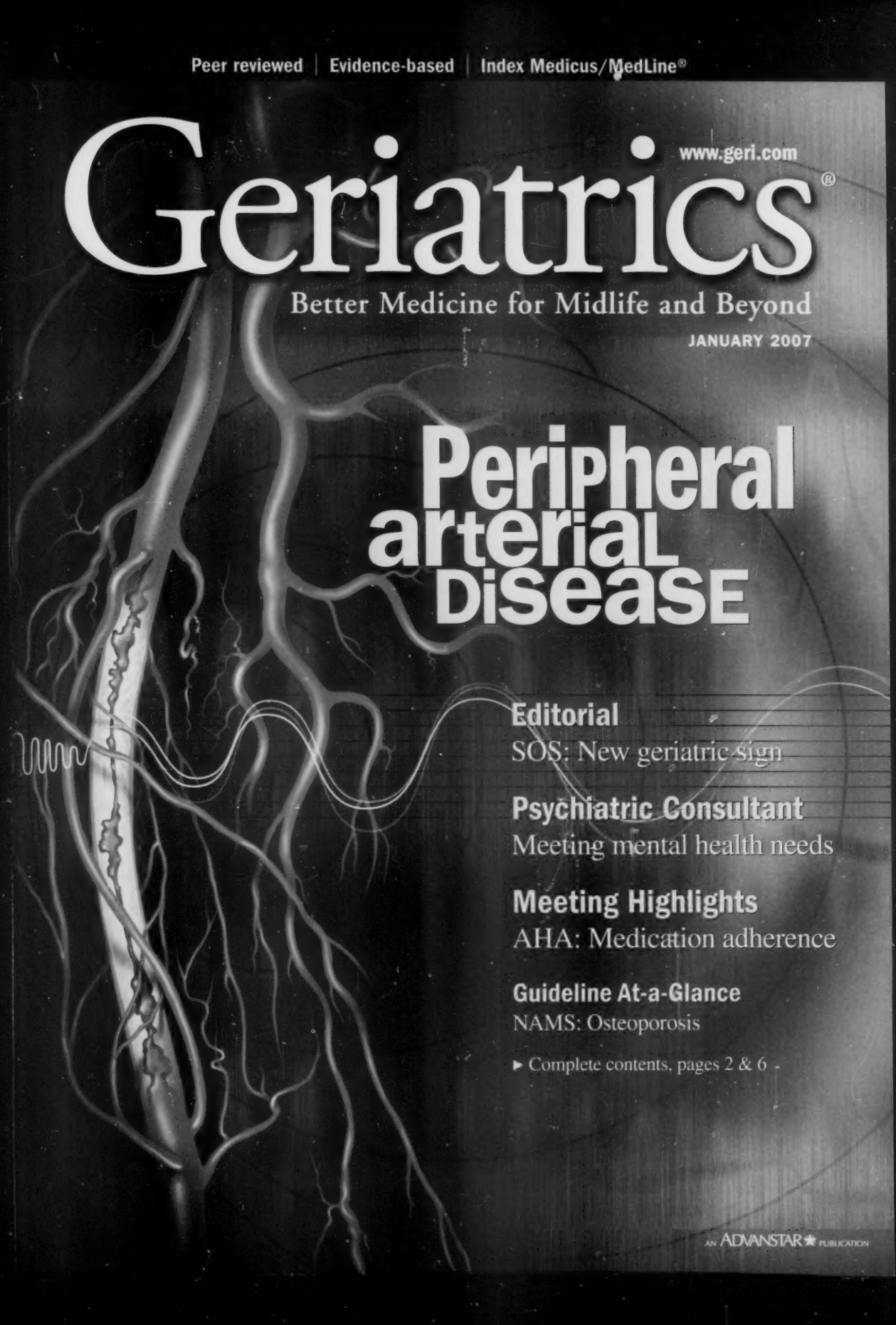
Better Medicine for Midlife and Beyond

JANUARY 2007



Peripheral arterial disease

Editorial
SOS: New geriatric sign

Psychiatric Consultant
Meeting mental health needs

Meeting Highlights
AHA: Medication adherence

Guideline At-a-Glance
NAMS: Osteoporosis

► Complete contents, pages 2 & 6

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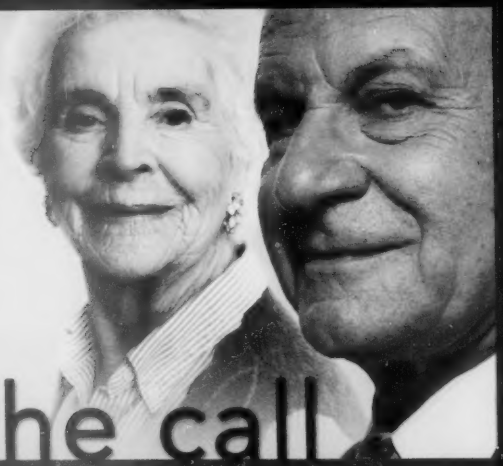

you make the call

An Interactive Case-based CME Program on Overactive Bladder

FACULTY

MATT T. ROSENBERG, MD

Family Physician
Mid-Michigan Center for Continence
Mid-Michigan Health Centers
Jackson, Michigan

TO PARTICIPATE, VISIT WWW.GERI.COM/OAB

TARGET AUDIENCE
This activity is intended for primary care physicians and ob/gyns.

STATEMENT OF NEED
An estimated 33 million adults in the United States are affected by the symptoms of overactive bladder (OAB), a disabling condition that impacts health-related quality of life. While the prevalence of OAB is relatively high and increases with age, many sufferers do not seek medical treatment. As the population ages, the prevalence of OAB is expected to increase. The process of micturition is both elegant and complex and can be disrupted at multiple points. It is important for physicians to understand the underlying pathophysiology of OAB. New research has shed light on the role of urothelial signaling as an important component of the micturition pathway, revealing new insights into the mechanism of action of antimuscarinic therapies for the treatment of OAB symptoms. Often, effective treatment is limited by problems with adherence to therapies and their side effects. Physicians need to appreciate the differences between currently available therapies in order to better individualize patient care.

LEARNING OBJECTIVES
Upon completion of this educational activity, participants should be able to:
- Review the diagnostic measures for OAB
- Assess the differences between currently available therapies for the treatment of OAB symptoms
- Describe important factors to consider when selecting a treatment regimen for a patient with the symptoms of OAB

ACCREDITATION STATEMENT
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Mission

Geriatrics provides practical, peer-reviewed, clinical guidance that today's time-stressed primary care physicians can use to improve the health and quality of life for older adults.

The editors of *Geriatrics* seek physician-authored review articles relating to the clinical care of patients age 50 and older. Visit www.geri.com for author guidelines.

PUBLISHER
Kerry Robinson
(201) 690-5435
kerry.robinson@advanstar.com

NATIONAL ACCOUNT MANAGER
John Currid
(973) 847-5323
jcurrid@advanstar.com

GROUP EDITOR
Deborah Kaplan
(201) 690-5434
dkaplan@advanstar.com

MANAGING EDITOR
Stephanie Davis
(440) 891-2657
sdavis@advanstar.com

SENIOR ART DIRECTOR
Peter R. Seltzer

ART DIRECTOR
Brian M. Smith

NEWS EDITOR
Barbara Bower

ADMINISTRATIVE ASSISTANT
Rae Ann Houghton

PRODUCTION MANAGER
Jane Dzuck
131 West First Street
Duluth, MN 55802
(218) 740-6313
jdzuck@advanstar.com

PRODUCTION DIRECTOR
Debi Harmer

CIRCULATION MANAGER
Melissa Feiro

SUBSCRIPTIONS
(888) 527-7008
fulfill@superfill.com

PERMISSIONS
Barry Gilbert
(440) 891-2707

REPRINTS
Jill Kaletha
(800) 344-8915 ext 168

DIRECT MAIL LIST
Renee Schuster
(800) 225-4569 Ext. 3113

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Editorial Board

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fsherman@advanstar.com

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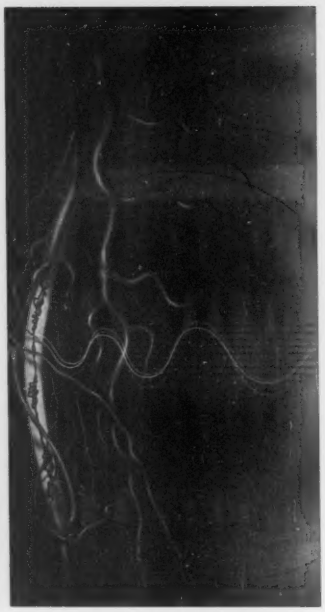
JANUARY 2007

Contents

REFERENCED IN INDEX MEDICUS/MEDLINE, CURRENT CONTENTS

Volume 62, Number 1

▶ COVER ARTICLE



19 Peripheral arterial disease
Cover illustration by Alexandra Baker

REFEREED CLINICAL ARTICLES

Cardiovascular Disorders

19 Peripheral arterial disease

Management of peripheral arterial disease in the elderly

Wilbert S. Aronow, MD

Peripheral arterial disease (PAD) in the elderly can be: 1) asymptomatic, 2) associated with intermittent claudication, or 3) cause critical limb ischemia. Persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from coronary artery disease (CAD). Antiplatelet drugs (eg, aspirin, clopidogrel, angiotensin-converting enzyme [ACE] inhibitors, statins) should be given to all persons with PAD. Beta blockers should be given if CAD is present. Exercise rehabilitation programs and cilostazol lengthen exercise time until leg pain develops.

Psychiatric Consultant

26 Meeting the mental health needs of older adults

Implications for primary care practice

Bradley Karlin, PhD • Jon D. Fuller, MD, AGSF

Greater attention to the mental health needs of older adults is critical in light of recent research documenting substantial undertreatment of mental health problems in late life. As often the first and only point of professional contact for mentally ill older adults, primary care physicians have an important and unique role in reducing enduring unmet mental health needs in late life. This article reviews the current state of geriatric mental health care delivery and provides valuable information and resources for use in clinical practice to increase and enhance primary care detection, treatment, and referral of psychological problems in older patients.

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POST-STROKE SPASTICITY

THE WEMOVE CLINICIANS' GUIDE TO POST-STROKE SPASTICITY MANAGEMENT

Use the link to connect to:

▶ Pathophysiology, diagnosis, and assessment of post-stroke spasticity (1 hr AMA category 1)

▶ Development of the treatment and rehabilitation plan in post-stroke spasticity (2 hrs)

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Start and stay with nonscheduled Rozerem—ZERO evidence of abuse or dependence

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- **First and only**—prescription insomnia medication that targets the normal sleep-wake cycle[1]
- **First and only**—prescription insomnia medication with no evidence of abuse potential in clinical studies[1]
- **First and only**—prescription insomnia medication that does not promote sleep by CNS depression[1]
- **Promote sleep with Rozerem**—patients who took Rozerem fell asleep faster than those who took placebo[1]
- **One simple 8-mg dose**[1]

*Rozerem is not a controlled substance. A clinical abuse liability study showed no differences indicative of abuse potential between Rozerem and placebo at doses up to 20 times the recommended dose (N=14). Three 35-day insomnia studies showed no evidence of rebound insomnia or withdrawal symptoms with Rozerem compared to placebo (N=2082).[1]

Please visit www.rozerem.com

Rozerem is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Rozerem can be prescribed for long-term use. Rozerem should not be used in patients with hypersensitivity to any components of the formulation, severe hepatic impairment, or in combination with fluvoxamine. Failure of insomnia to remit after a reasonable period of time should be medically evaluated, as this may be the result of an unrecognized underlying medical disorder. Hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Rozerem has not been studied in patients with severe sleep apnea, severe COPD, or in children or adolescents. The effects in these populations are unknown. Avoid taking Rozerem with alcohol. Rozerem has been associated with decreased testosterone levels and increased prolactin levels. Health professionals should be mindful of any unexplained symptoms possibly associated with such changes in these hormone levels. Rozerem should not be taken with or immediately after a high-fat meal. Rozerem should be taken within 30 minutes before going to bed and activities confined to preparing for bed. The most common adverse events seen with Rozerem that had at least a 2% incidence difference from placebo were somnolence, dizziness, and fatigue.

Please see adjacent Brief Summary of Prescribing Information.

Rozerem™
ramelteon 8-mg tablets

Proven for sleep.
Nonscheduled for added safety.

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Rozerem®
ramelteon 8-mg tablets

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Brief Summary of Prescribing Information
05-1114

ROZEREM™
(ramelteon) Tablets

INDICATIONS AND USAGE
ROZEREM is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS
ROZEREM is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ROZEREM formulation.

WARNINGS
Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM during the clinical development program.

ROZEREM should not be used by patients with severe hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine (see **PRECAUTIONS: Drug Interactions**).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS
General
ROZEREM has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Use in Adolescents and Children
ROZEREM has been associated with an effect on reproductive hormones in adults, e.g. decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans (see **Pediatric Use**).

Information for Patients
Patients should be advised to take ROZEREM within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed.

Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

Patients should be advised that they should not take ROZEREM with or immediately after a high fat meal.

Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.

Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

Laboratory Tests
No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate.

Drug Interactions
ROZEREM has a highly variable inter-subject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ROZEREM; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

Effects of Other Drugs on ROZEREM Metabolism
Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ROZEREM 16 mg and fluvoxamine, the $AUC_{0\text{-}\infty}$ for ramelteon increased approximately 190-fold, and the C_{max} increased approximately 70-fold, compared to ROZEREM administered alone. ROZEREM should not be used in combination with fluvoxamine (See WARNINGS). Other less potent CYP1A2 inhibitors have not been adequately studied. ROZEREM should be administered with caution to patients taking less strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon and metabolite M-II, (both $AUC_{0\text{-}\infty}$ and C_{max}) after a single 32 mg dose of ROZEREM. Efficacy may be reduced when ROZEREM is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor): The $AUC_{0\text{-}\infty}$ and C_{max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16 mg dose of ROZEREM was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of ROZEREM alone. Similar increases were seen in M-II pharmacokinetic variables. ROZEREM should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor): The total and peak systemic exposure ($AUC_{0\text{-}\infty}$ and C_{max}) of ramelteon after a single 16 mg dose of ROZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. ROZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

Effects of ROZEREM on Metabolism of Other Drugs
Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 (S)/CYP1A2 (R) substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

Effect of Alcohol on ROZEREM
Alcohol: With single-dose, daytime co-administration of ROZEREM 32 mg and alcohol (0.6 g/kg), there were no clinically meaningful or statistically significant effects on peak or total exposure to ROZEREM. However, an additive effect was seen on some measures of psychomotor performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog Scale of sedation) at some post-dose time points. No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of ROZEREM is to promote sleep, patients should be cautioned not to consume alcohol when using ROZEREM.

Drug/Laboratory Test Interactions
ROZEREM is not known to interfere with commonly used clinical laboratory tests. In addition, *in vitro* data indicate that ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenesis
In a two-year carcinogenicity study, B6C3F$_1$ mice were administered ramelteon at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥ 300 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area-under-the-curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 60, 250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testis at dose levels ≥ 250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥ 60 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1,429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24 hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis
Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma TK$^{+/-}$ cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and in *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility
Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m^2 basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females at ≥ 60 mg/kg/day (79-times higher than the MRHD on a mg/m^2 basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥ 60 mg/kg/day, but no effects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m^2 basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m^2 basis) when considering all studies.

Pregnancy: Pregnancy Category C
Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose [MRHD] on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area-under-the-curve [AUC] comparison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,862-times and 99-times higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from day 6 of gestation through parturition to postnatal (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased adrenal gland weight. Reduced body weight during the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an alteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and postnatal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m^2 basis).

Labor and Delivery
The potential effects of ROZEREM on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. ROZEREM has no established use in labor and delivery.

Nursing Mothers
Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ROZEREM in nursing mothers is not recommended.

Pediatric Use
Safety and effectiveness of ROZEREM in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

Geriatric Use
A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ROZEREM were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS
Overview
The data described in this section reflect exposure to ROZEREM in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment
Five percent of the 3594 individual subjects exposed to ROZEREM in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ROZEREM were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials
The incidence of adverse events during the Phase 1 through 3 trials (% placebo, n=1370; % ramelteon [8 mg], n=1250) were: headache NOS (7%, 7%), somnolence (3%, 5%), fatigue (2%, 4%), dizziness (3%, 5%), nausea (2%, 3%), insomnia exacerbated (2%, 3%), upper respiratory tract infection NOS (2%, 3%), diarrhea NOS (2%, 2%), myalgia (1%, 2%), depression (1%, 2%), dysgeusia (1%, 2%), arthralgia (1%, 2%), influenza (0, 1%), blood cortisol decreased (0, 1%)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

DRUG ABUSE AND DEPENDENCE
ROZEREM is not a controlled substance.

Human Data: See the CLINICAL TRIALS section, Studies Pertinent to Safety Concerns for Sleep-Promoting Agents in the Complete Prescribing Information.

Animal Data. Ramelteon did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys did not self-administer ramelteon and the drug did not induce a conditioned place preference in rats. There was no generalization between ramelteon and midazolam. Ramelteon did not affect rotorod performance, an indicator of disruption of motor function, and it did not potentiate the ability of diazepam to interfere with rotorod performance.

Discontinuation of ramelteon in animals or in humans after chronic administration did not produce withdrawal signs. Ramelteon does not appear to produce physical dependence.

OVERDOSAGE
Signs and Symptoms
No cases of ROZEREM overdose have been reported during clinical development.

ROZEREM was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen.

Recommended Treatment
General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed.

Hemodialysis does not effectively reduce exposure to ROZEREM. Therefore, the use of dialysis in the treatment of overdosage is not appropriate.

Poison Control Center
As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdosage.

Rx only

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Manufactured in:
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Marketed by:
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Lincolnshire, IL 60069

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References: 1. Rozerem package insert, Takeda Pharmaceuticals America, Inc. 2. Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative side effects. *Arch Gen Psychiatry*. In press.

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Geriatrics®

Better Medicine for Midlife and Beyond

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Limit references to 20 citations. Cite references in the text in numerical sequence. Please follow AMA style. Type all references on a separate sheet.

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Contents

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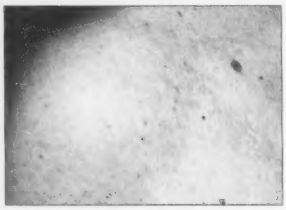
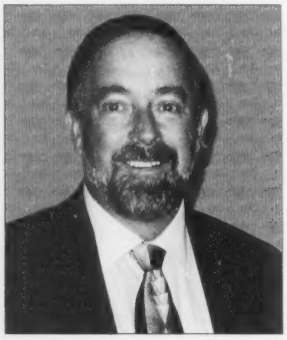
9 Dr. Sherman/Editorial



18 Derm DDx



36 Medicare Matters

DEPARTMENTS

5 Information for Authors

9 Editorial
SOS:Sock/Stocking On Sign

14 News & Views
Folic acid can reduce risk of heart disease
Lower systolic BP in patients with HF could mean higher risk of death
No increased risk of heart disease in women on low-carb diet

Visit www.geri.com for an additional news brief:
Anxiety related to physical disease and disability, poor quality of life

15 Guideline At-a-Glance
NAMS: Osteoporosis guideline

16 Meeting Highlights: AHA
Pharmacist intervention improves medication adherence in elderly
Low testosterone increases CHD risk in older women
Fluvastatin XL/ezetimibe combo well tolerated in certain statin users

18 Derm DDx
Norman Levine, MD
Patient has year-round history of itchy eruptions on neck and trunk

36 Medicare Matters
Don Self
Outdated charts can lead to billing complications

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For adult patients with **CHRONIC IDIOPATHIC CONSTIPATION**

Relief

takes a different direction

Targeted chloride channel activation that delivers

- Up to 71% of patients achieved normal bowel function (≥3 SBMs* per week)†[1]
- Proven long-term safety profile demonstrated in 6-month and 12-month safety studies[2]
- The **ONLY** agent approved for adults with chronic idiopathic constipation that includes those 65 years and older

Important Safety Information

- AMITIZA is indicated for the treatment of chronic idiopathic constipation in the adult population.
- AMITIZA should not be used in patients with a known hypersensitivity to any components of the formulation and in patients with a history of mechanical gastrointestinal obstruction. Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating AMITIZA treatment.
- The safety of AMITIZA in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. AMITIZA should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with AMITIZA and should be capable of complying with effective contraceptive measures.
- AMITIZA should not be administered to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. If the diarrhea becomes severe, patients should consult their health professional.
- In clinical trials, the most common adverse event was nausea (31%). Other adverse events (≥5% of patients) included diarrhea (13%), headache (13%), abdominal distention (7%), abdominal pain (7%), flatulence (6%), sinusitis (5%) and vomiting (5%).

Relief is defined as ≥3 SBMs per week.

Please see Brief Summary of Prescribing Information on adjacent page.

*Spontaneous bowel movements.

†In 4-week clinical studies. Placebo: 44%-53%.

References: 1. Data on file, Sucampo Pharmaceuticals, Inc. **2.** AMITIZA [package insert]. Bethesda, Md: Sucampo Pharmaceuticals, Inc.; 2006.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION-
Please see package insert for complete prescribing information
720-03565

AMITIZA™
(lubiprostone)
Soft Gelatin Capsules

INDICATIONS AND USAGE

AMITIZA™ is indicated for the treatment of chronic idiopathic constipation in the adult population.

CONTRAINDICATIONS

AMITIZA™ is contraindicated in those patients with a known hypersensitivity to the drug or any of its excipients, and in patients with a history of mechanical gastrointestinal obstruction.

WARNINGS

Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating AMITIZA™ treatment.

The safety of AMITIZA™ in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. AMITIZA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with AMITIZA™ and should be capable of complying with effective contraceptive measures (see ***Teratogenic Effects: Pregnancy Category C)***.

PRECAUTIONS

Patient Information:

AMITIZA™ may cause nausea. If this occurs, concomitant administration of food with AMITIZA™ may reduce symptoms of nausea. AMITIZA™ should not be administered to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. If the diarrhea becomes severe consult your physician.

Drug Interactions:

Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug–drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to M3. Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies in primary cultures of human hepatocytes show no induction of the cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4. No additional drug–drug interaction studies have been performed. Based on the available information, no protein binding–mediated drug interactions of clinical significance are anticipated.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose.

Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y TK+/–) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the *in vivo* mouse bone marrow micronucleus assay.

Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1000 mcg/kg/day dose in rats is approximately 166 times the recommended human dose of 48 mcg/day, based on the body surface area.

Teratogenic Effects: Pregnancy Category C:

Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats and rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of AMITIZA™ at 24 mcg BID, four women became pregnant. Per protocol, AMITIZA™ was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

AMITIZA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers:

It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

AMITIZA™ has not been studied in pediatric patients.

ADVERSE REACTIONS

In clinical trials, 1429 patients received AMITIZA™ 24 mcg BID or placebo. Table 1 presents data for the adverse experiences that were reported in at least 1% of patients who received AMITIZA™ and that occurred more frequently on study drug than placebo. It should be noted that the placebo data presented are from short-term exposure (≤4 weeks) whereas the AMITIZA™ data are cumulative data that were collected over 3- or 4-week, 6-month, and 12-month observational periods and that some conditions are common among otherwise healthy patients over a 6- and 12-month observational period.

Table 1: Adverse Events Reported for Patients Treated with AMITIZA™

System/Adverse Experience	Placebo n = 396 %	AMITIZA™ 24 mcg QD n = 39 %	AMITIZA™ 24 mcg BID n = 113 %	AMITIZA™ Any Active Dose† n = 1175 %
Gastrointestinal disorders				
Nausea	5.1	17.2	31.1	30.9
Diarrhea	9.9	10.3	13.2	13.2
Abdominal distension	2.2	0.0	7.1	6.6
Abdominal pain	2.5	2.4	6.7	6.6
Flatulence	1.8	2.4	5.1	5.9
Vomiting	0.5	0.0	4.6	4.4
Loose stools	0.0	0.0	3.4	3.2
Dyspepsia	1.3	0.0	2.5	2.7
Abdominal pain upper	1.5	0.0	2.2	2.1
Abdominal pain lower	0.5	0.0	1.5	1.6
Gastroesophageal reflux disease	0.6	0.0	1.8	1.7
Abdominal discomfort	0.5	2.4	1.5	1.5
Dry mouth	0.3	0.0	1.5	1.4
Constipation	0.5	0.0	1.1	1.0
Stomach discomfort	0.3	0.0	1.1	1.0
Infections and infestations				
Sinusitis	1.6	0.0	4.9	4.0
Urinary tract infections	1.9	2.4	4.4	4.3
Upper respiratory tract infection	0.5	0.0	2.7	3.6
Nasopharyngitis	2.2	0.0	2.9	2.7
Influenza	0.5	0.0	2.0	1.9
Bronchitis	0.3	2.4	1.5	1.7
Gastroenteritis viral	0.0	2.4	1.0	1.0
Viral infection	0.3	2.4	0.5	0.9
Nervous system disorders				
Headache	5.6	2.4	13.2	13.0
Dizziness	1.3	2.4	4.1	4.0
Hypoesthesia	0.0	2.4	0.5	0.6
General disorders and administration conditions				
Edema peripheral	0.3	0.0	3.8	3.6
Fatigue	1.5	5.9	2.3	2.5
Chest discomfort	0.0	2.4	1.5	1.6
Chest pain	0.0	0.0	1.1	1.0
Pyrexia	0.3	0.0	1.1	1.0
Musculoskeletal and connective tissue disorders				
Arthralgia	0.3	0.0	3.1	3.0
Back pain	0.8	2.4	2.3	2.3
Pain in extremity	0.0	2.4	1.9	1.9
Muscle cramp	0.0	0.0	1.0	0.9
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	0.0	2.4	2.4	2.5
Pharyngolaryngeal pain	2.2	0.0	1.7	1.5
Cough	0.8	0.0	1.6	1.5
Investigations				
Weight increased	0.0	0.0	1.0	0.9
Psychiatric disorders				
Depression	0.0	0.0	1.4	1.4
Anxiety	0.3	0.0	1.4	1.6
Insomnia	0.0	0.0	1.4	1.4
Vascular disorders				
Hypertension	0.0	0.0	1.0	0.9

†Includes patients dosed at 24 mcg QD, 24 mcg BID, and 24 mcg TID

AMITIZA™-induced Nausea:

Among constipated patients, 31.1% of those receiving AMITIZA™ 24 mcg BID reported nausea. Of those patients, 3.4% reported severe nausea and 8.7% discontinued treatment due to nausea. It should be noted that the incidence of nausea increased in a dose-dependent manner with the lowest overall incidence for nausea seen at the 24 mcg QD dose (17.2%). Further analysis of nausea has shown that long-term exposure to AMITIZA™ does not appear to place patients at elevated risk for experiencing nausea. In the open-label, long-term studies, patients were allowed to titrate the dose of AMITIZA™ down to 24 mcg QD from 24 mcg BID if experiencing nausea. It should also be noted that nausea decreased when AMITIZA™ was administered with food and that, across all dose groups, the rate of nausea was substantially lower among constipated men (13.2%) and constipated elderly patients (18.6%) when compared to the overall rate (30.9%). No patients in the trials were hospitalized due to nausea.

AMITIZA™-induced Diarrhea:

Among constipated patients, 13.2% of those receiving AMITIZA™ 24 mcg BID reported diarrhea. Of those patients, 3.4% reported severe diarrhea and 2.2% discontinued treatment due to diarrhea. The incidence of diarrhea did not appear to be dose-dependent. No serious adverse events were reported for electrolyte imbalance in the six clinical trials and no clinically significant changes were seen in serum electrolyte levels while patients were receiving AMITIZA™.

Other Adverse Events:

The following list of adverse events include those that were considered by the investigator to be possibly related to AMITIZA™ and reported more frequently (>0.2%) on AMITIZA™ than placebo and those that lead to discontinuation more frequently (≥0.2%) on AMITIZA™ than placebo. Although the events reported occurred during treatment with AMITIZA™, they were not necessarily attributed to dosing of AMITIZA™:

- **Gastrointestinal disorders:** watery stools, fecal incontinence, abnormal bowel sounds, frequent bowel movements, retching
- **Nervous system disorders:** syncope, tremor, dysgeusia, paraesthesia
- **General disorders and administration site conditions:** rigors, pain, asthenia, malaise, edema
- **Respiratory, thoracic, and mediastinal disorders:** asthma, painful respiration, throat tightness
- **Skin and subcutaneous tissue disorders:** hyperhidrosis, urticaria, rash
- **Psychiatric disorders:** nervousness
- **Vascular disorders:** flushing, palpitations
- **Metabolism and nutrition disorders:** decreased appetite
- **Ear and labyrinth disorders:** vertigo

Overdosage:

There have been two confirmed reports of overdosage with AMITIZA™. The first report involved a 3-year-old child who accidentally ingested 7 to 8 capsules of 24 mcg of AMITIZA™ and fully recovered. The second report was a study subject who self-administered a total of 96 mcg AMITIZA™ per day for 8 days. The subject experienced no adverse events during this time. Additionally, in a definitive Phase 1 cardiac repolarization study, 51 patients administered a single oral dose of 144 mcg of AMITIZA™, which is 6 times the normal single administration dose. Thirty-nine (39) of the 51 patients experienced an adverse event. The adverse events reported in >1% of this group included the following: nausea (45.1%), vomiting (27.5%), diarrhea (25.5%), dizziness (17.6%), loose or watery stools (13.7%), headache (11.8%), retching (7.8%), abdominal pain (5.9%), flushing or hot flush (5.9%), dyspnea (3.9%), pallor (3.9%), stomach discomfort (3.9%), syncope (3.9%), upper abdominal pain (2.0%), anorexia (2.0%), asthenia (2.0%), chest discomfort (2.0%), dry mouth (2.0%), hyperhidrosis (2.0%), skin irritation (2.0%), and vasovagal episode (2.0%).

DOSAGE AND ADMINISTRATION

The recommended dosage for AMITIZA™ is 24 mcg taken twice daily (BID) orally with food. Physicians and patients should periodically assess the need for continued therapy.

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and
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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SOS: Sock/Stocking On Sign

A new geriatric sign predicts ability to dress independently

Fredrick T. Sherman, MD, MSc
Medical Editor

"Always note and record the unusual. Keep and compare your observations. Communicate or publish short notes on anything that is striking or new. Do not waste your time in compilations, but when your observations are sufficient, do not let them die with you." [1]

Dr. Sherman
is professor of geriatrics and medicine, The Brookdale Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, and medical director for Senior Health Partners, New York.

Send comments
to Dr. Sherman at
fsherman@advanstar.com
fax to 800-788-7188

My foot fetish is well known to those who regularly amble through this column. At various times in the past 6 years, I have written about the physiologic and, more commonly, pathologic aspects of pedal health in my older patients. I have watched thousands of seniors struggle to remove and replace their shoes and socks/stockings in preparation for a thorough evaluation of their feet. Based on these observations, I have suggested new ways to prevent cellulitis and diagnose chronic aortic regurgitation.[2,3] I have also shared a mnemonic, the ABCDEFG's of diabetes, to help you deliver comprehensive care to your elderly diabetic patients, where "F" is for foot care.[4]

Now, I am proposing a new geriatric sign that predicts the ability to successfully dress independently. To appreciate the significance of this clinical sign, it is critical to understand how women and men undress and dress themselves. Based on my observations, seated older women and men of the current generation use different techniques to reach their feet in order to take off and put on their stockings or socks. None of these observations or conclusions applies to older women who wear pantyhose or to older men or women who use a wheelchair.

Most older women who walk into the office wear a dress or skirt. They typically reach each foot by bending at the waist (trunk forward flexion) and flexing their hip and knee so as not to cross their legs. Then, they remove their shoe and stocking, usually a "knee high" stocking, with one or two hands.

Most older men, on the other hand, will reach each foot by crossing one leg over the other, ie, externally rotating their hip, flexing their knee, and placing the lower leg over the opposite knee. Once the older man reaches his foot, he removes his shoe and sock, as the older woman removes her shoe and stocking. The older woman who wears pants will often cross one leg over the other, just like the older man.

Putting the sock/stocking back on, however, regardless of gender and method used to reach each foot, always requires use of two hands, as it is the most difficult component subtask of successfully dressing oneself. I have correlated using two hands to successfully put on a sock or stocking as indicating that older adults of either gender, who walk with or without an assistive device, can dress independently. If they

cannot don the sock/stocking using two hands then they will need assistance in dressing.

I have called the successful donning of a sock/stocking using two hands a positive "Sock/stocking On Sign-x" (**SOS-x**), where the "x" means one leg crossed over another (figure, left) and a positive "Sock/stocking On Sign-ll"(**SOS-ll**), where "ll" means the legs are kept parallel and not crossed (figure, right). A positive **SOS-x** or **SOS-ll** may be unilateral or bilateral. For example, arthritis or previous surgery in one hip may limit the ability to cross the legs, making **SOS-ll** the preferred technique. A positive bilateral **SOS-x** or **SOS-ll** or one of each, **SOS-x/SOS-ll**, indicates independence in dressing in seniors who walk with or without an assistive device.

Seniors who demonstrate positive bilateral **SOS**'s in any combination, should be asked: "How much difficulty do you have dressing?" Those who claim "some" or "a lot" of difficulty are at high risk to need help with dressing in the future.[5] They should be evaluated for multiple, treatable and possibly reversible impairments that could affect successful dressing, eg, osteoarthritis of the hips, shoulders, and knees, quadriceps weakness from vitamin D deficiency and/or disuse, or visual deficits.[6]

Rarely in my clinical practice has using an assistive device, eg, a sock or stocking donner, allowed an elderly patient to be independent in dressing and bathing. So needing help with dressing or bathing requires a caregiver.[7]

There is substantial evidence that both aerobic exercise and strength training are of benefit to the bodies and minds of older adults.[8-10] I believe that adding flexibility exercises consisting of upper extremity range of motion, flexion at the waist (trunk forward flexion) and at the hips and knees, and external rotation of the hips will maintain the dressing skills of both men and women. "If you don't use your dressing skills, you will lose them" is a warning I give to my older patients, recognizing that these range of motion exercises should be performed daily as they are the key to independently dressing.

Figure (left): a man crossing his leg to successfully put on a sock using both hands, a positive left **SOS-x**

Figure (right): a woman donning a stocking using both hands, while keeping both legs parallel and perpendicular to the floor, a positive right **SOS-ll**

While the **SOS-x** and **SOS-ll** may be gender specific in the current generation of older adults, future generations of men and women may put on their socks/stockings using similar techniques. This new geriatric sign needs to be validated and studied to determine its sensitivity, specificity and positive predictive value for independent dressing. The **SOS-x** and **SOS-ll** should be evaluated, perhaps with a balance test, as a predictor of independent bathing.[11]

With the massive bolus of baby boomers moving toward old age, maintaining their ability to dress and bathe will assure longer independence, and limit the need for premature caregiving.

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Treat the symptoms of depression your patients talk about, and those they don't. Many times, patients don't mention some of their symptoms because they don't realize they are related. That's where Cymbalta can help. Cymbalta treats the emotional, anxious, and painful somatic symptoms of depression.[1a-c,2*] To learn more about treating beyond the obvious, visit www.insidecymbalta.com

*Cymbalta 60 mg/day vs placebo ($P \leq .05$) by MMRM for major depressive disorder on mean change in HAM-D_{17} Total Score, Maier Subscale, Psychic Anxiety, and Visual Analog Scale. Full antidepressant response may take 4-6 weeks.
MMRM=Mixed-effects Models Repeated Measures analysis

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a: CYM20060101A; b: CYM20060101B; c: CYM20050315S.
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treat beyond the obvious

Cymbalta® DELAYED RELEASE CAPSULES
duloxetine HCl

Important Safety Information

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.**
- **Cymbalta is not approved for use in pediatric patients.**

Cymbalta should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or thioridazine and not in patients with a known hypersensitivity or with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All adult and pediatric patients being treated with an antidepressant for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially when initiating drug therapy and when increasing or decreasing the dose. A health professional should be immediately notified if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication.

Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs, including triptans. Concomitant use is not recommended.

Cymbalta should not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (CrCl <30 mL/min).

Postmarketing, severe elevations of liver enzymes or liver injury with a hepatocellular, cholestatic, or mixed pattern have been reported.

Cymbalta should generally not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Cases of orthostatic hypotension and/or syncope as well as cases of hyponatremia have been reported.

Most common adverse events (≥5% and at least twice placebo) in MDD premarketing clinical trials were: nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating. Most common adverse events in diabetic peripheral neuropathic pain (DPNP) premarketing clinical trials were: nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia.

See Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent page.

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CYMBALTA®

(duloxetine hydrochloride) Delayed-release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

WARNING

Suicidality in Children and Adolescents—Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. (*See* WARNINGS *and* PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

INDICATIONS AND USAGE: Cymbalta is indicated for the treatment of major depressive disorder (MDD). Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN).

CONTRAINDICATIONS: ***Hypersensitivity***—Known hypersensitivity to duloxetine or any of the inactive ingredients. ***Monoamine Oxidase Inhibitors (MAOIs)***—Concomitant use with Cymbalta is contraindicated (*see* WARNINGS). ***Uncontrolled Narrow-Angle Glaucoma***—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use is not recommended in patients with uncontrolled narrow-angle glaucoma.

WARNINGS: Clinical Worsening and Suicide Risk—Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, ie, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face to face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS, Discontinuation of Treatment with Cymbalta).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta is not approved for use in treating bipolar depression.

MAOIs—In patients receiving a serotonin reuptake inhibitor (SSRI) in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRIs and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

Serotonin Syndrome—The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated (*see* CONTRAINDICATIONS *and* WARNINGS).

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* PRECAUTIONS, Drug Interactions).

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended (*see* PRECAUTIONS, Drug Interactions).

PRECAUTIONS: ***General***—Hepatotoxicity—Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively. Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease. Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors (*see* CLINICAL PHARMACOLOGY, Drug-Drug Interactions, *and* PRECAUTIONS, Drug Interactions) and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy. Effect on Blood Pressure—In MDD clinical trials, Cymbalta treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0-6.8 bpm and increases in mean blood pressure were 4.7-6.8 mm Hg (systolic) and 4.5-7 mm Hg (diastolic) up to 12 hours after dosing. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes). Activation of Mania/Hypomania—In placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (1/1139) of Cymbalta-treated patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of MDD. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania. Seizures—Cymbalta has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with MDD, seizures occurred in 0.1% (1/1139) of Cymbalta-treated patients and 0% (0/777) of placebo treated patients. In placebo-controlled clinical trials in patients with diabetic peripheral neuropathy, seizures did not occur in any patients treated with either Cymbalta or placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder. Hyponatremia—Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported and appeared to be reversible when Cymbalta was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted. Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma (*see* CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma). Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in MDD placebo-controlled clinical trials of up to 9 weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 321 patients who received Cymbalta in MDD placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; Cymbalta was not associated with the development of clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes). In DPN placebo-controlled clinical trials, Cymbalta-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (*see* ADVERSE REACTIONS, Electrocardiogram Changes). In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, small increases in fasting blood glucose were observed in Cymbalta-treated patients. HbA_{1c} was stable in both Cymbalta-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the Cymbalta and the routine care groups, but the mean increase was 0.3% greater in the Cymbalta-treated group. There was also a small increase in fasting blood glucose in the Cymbalta-treated group. Total cholesterol was increased in Cymbalta-treated patients (2 mg/dL) and decreased in the routine care group (6 mg/dL). Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients.

Laboratory Tests—No specific laboratory tests are recommended.

Drug Interactions—*Potential for Other Drugs to Affect Cymbalta*—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. Inhibitors of CYP1A2—Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided. Inhibitors of CYP2D6—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (eg, fluoxetine, quinidine). *Potential for Duloxetine to Affect Other Drugs*—Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates. Drugs Metabolized by CYP2D6—Cymbalta is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (eg, propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. *Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs*—Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (*see* PRECAUTIONS,

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Hepatotoxicity). CNS-Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action. Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta and the potential for serotonin syndrome, caution is advised when Cymbalta is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (*see* WARNINGS, Serotonin Syndrome). The concomitant use of Cymbalta with other SSRIs, SNRIs, or tryptophan is not recommended (*see* PRECAUTIONS, Drug Interactions). Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* WARNINGS, Serotonin Syndrome). Potential for Interaction with Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors—*See* CONTRAINDICATIONS *and* WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis). In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors. Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*. Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at daily doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

Pregnancy—Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development. When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rats; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rats; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits). When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) ; the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (*see* WARNINGS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established (*see* BOX WARNING *and* WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, Cymbalta has been associated with cases of clinically significant hyponatremia (*see* Hyponatremia, *under* PRECAUTIONS).

ADVERSE REACTIONS: Cymbalta has been evaluated for safety in 2418 patients diagnosed with MDD who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8 or 9 week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year. Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12 to 13 week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure. For both MDD and DPN clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. MedDRA terminology was used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo). Diabetic Peripheral Neuropathic Pain—Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials—Major Depressive Disorder—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of MDD placebo-controlled trials (N=1139 Cymbalta; N=777 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, vomiting; Metabolism and Nutrition Disorders—appetite decreased (includes anorexia); Investigations—weight decreased; General Disorders and Administration Site Conditions—fatigue; Nervous System Disorders—dizziness, somnolence, tremors; Skin and Subcutaneous Tissue Disorders—sweating increased; Vascular Disorders—hot flushes; Eye Disorders—vision blurred; Psychiatric Disorders—insomnia (includes middle insomnia), anxiety, libido decreased, orgasm abnormal (includes anorgasmia); Reproductive System and Breast Disorders—males only: erectile dysfunction, ejaculation delayed, ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure).

The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence ≤ placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating.

Diabetic Peripheral Neuropathic Pain—Treatment emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg QD; N=115 Cymbalta 20 mg QD; N=223 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; General Disorders and Administration Site Conditions—fatigue, asthenia, pyrexia; Infections and Infestations—nasopharyngitis; Metabolism and Nutrition Disorders—decreased appetite, anorexia; Musculoskeletal and Connective Tissue Disorders—muscle cramp, myalgia; Nervous System Disorders—somnolence, headache, dizziness, tremor; Psychiatric Disorders—insomnia; Renal and Urinary Disorders—pollakiuria; Reproductive System and Breast Disorders—erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis.

The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence ≤ placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; somnolence; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function—Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Sexual side effects spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials were: Males (N=378 Cymbalta; N=247 placebo): orgasm abnormal (includes anorgasmia), ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure), libido decreased, erectile dysfunction, ejaculation delayed. Females (N=761 Cymbalta; N=530 placebo): orgasm abnormal, libido decreased.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. Physicians should routinely inquire about possible sexual side effects. See Table 4 in full PI for specific ASEX results.

Urinary Hesitation—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

Laboratory Changes—Cymbalta treatment, for up to 9 weeks in MDD or 13 weeks in DPN placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS). ***Vital Sign Changes***—Cymbalta treatment, for up to 9 weeks in MDD placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg (*see* PRECAUTIONS). Cymbalta treatment, for up to 9 weeks in MDD placebo-controlled clinical trials and for up to 13 weeks in DPN placebo-controlled trials caused a small increase in heart rate compared to placebo of about 2 beats per minute. ***Weight Changes***—In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13 weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. ***Electrocardiogram Changes***—Electrocardiograms were obtained from 321 Cymbalta-treated patients with MDD and 169 placebo-treated patients in clinical trials lasting up to 8 weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between Cymbalta-treated and placebo-treated patients. Electrocardiograms were obtained from 528 Cymbalta-treated patients with DPN and 205 placebo-treated patients in clinical trials lasting up to 13 weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTc measurements between Cymbalta-treated and placebo-treated patients.

Postmarketing Spontaneous Reports—Adverse events reported rarely since market introduction that were temporally related to Cymbalta therapy include: hallucinations, rash, and urinary retention. The following adverse events were reported very rarely: alanine aminotransferase increased, alkaline phosphatase increased, anaphylactic reaction, angioneurotic edema, aspartate aminotransferase increased, bilirubin increased, extrapyramidal disorder, glaucoma, hepatitis, hypersensitivity, hypertensive crisis, hyponatremia, jaundice, mania, orthostatic hypotension (especially at the initiation of treatment), seizures, serotonin syndrome, Stevens-JohnsonSyndrome, supraventricular arrhythmia, syncope (especially at initiation of treatment), syndrome of inappropriate antidiuretic hormone secretion (SIADH), trismus, and urticaria.

DRUG ABUSE AND DEPENDENCE: ***Controlled Substance Class***—Duloxetine is not a controlled substance. ***Physical and Psychological Dependence***—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: There is limited clinical experience with Cymbalta overdose in humans. In premarketing clinical trials, cases of acute ingestions up to 1400 mg, alone or in combination with other drugs, were reported with none being fatal. Postmarketing experience includes reports of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg. Fatalities have been very rarely reported, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures. ***Management of Overdose***—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

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DID YOU see *these?*

NEWSWORTHY RESEARCH patients may be asking about

Folic acid can reduce risk of heart disease

"Folic acid is a much undervalued vitamin...the evidence that it can reduce the risk of heart attack and stroke is becoming increasingly persuasive," said lead author David S. Wald, MD, senior lecturer and consultant cardiologist, Centre for Environmental and Preventive Medicine, Wolfson Institute of Preventative Medicine, Barts, and The London Queen Mary's School of Medicine and Dentistry, London.

In meta-analyses of available studies (cohort and genetic studies) examining the relationship between homocysteine and cardiovascular disease (CVD), Dr. Wald and colleagues identified homocysteine as a cause of CVD. Folic acid is known to reduce homocysteine concentrations.

The addition of 0.8 mg/d of folic acid showed a 3 µmol/l decrease in serum homocysteine, which reduced the risk of MI by 15% and stroke by 24%.

Based on the findings, the evidence supports a protective cardiovascular effect with use of folic acid.

Source: BMJ 2006; 333(7578):1114-7.

Lower systolic BP in patients with HF could mean higher risk of death

Low systolic pressure in patients with heart failure (HF) has shown to be a key predictor of mortality, according to lead author Gregg C. Fonarow, MD, The Eliot Corday Chair in Cardiovascular Medicine and Science, principal investigator and director, Ahmanson-University of California, Los Angeles, Cardiomyopathy Center, and colleagues.

In a retrospective study of 48,612 HF patients enrolled in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), the mortality rate for patients with systolic BP < 120 mm/Hg was 7.2%. Mortality rates were 3.6% for systolic BP 120 - 139 mm/Hg; 2.5% for pressures 140 - 161 mm/Hg; and 1.7% for those with systolic pressures >161 mm/Hg. Mean age was 73.1 years.

In a press release, Dr. Fonarow said, "Systolic blood pressure (SBP) taken at hospital admission was a strong independent predictor of mortality and morbidity in this large heart failure patient population. We hope the findings may help clinicians effectively stratify risk and offer more targeted treatments based on a patient's SBP level."

The authors said traditional thought was that most patients with HF presented to the hospital with lower systolic BP, but the study revealed higher systolic BP (> 140 mm/Hg) in more than 50% of patients.

Dr. Fonarow said to optimize treatment, HF patients may need different approaches depending whether their SBP is normal, low, or high.

The study was funded by GlaxoSmithKline.

SOURCE: JAMA 2006; 296(18): 2217-26.

No increased risk of coronary heart disease in women on low-carb diet

A study of 82,802 women in the Nurses' Health Study failed to reveal an association between low carbohydrate/high-protein and high-fat diets with increased risk of coronary heart disease (CHD). In fact, when fats and protein were derived from vegetable sources, risk of CHD was lowered.

Using a diet score based on self-reported food intake, participants were divided into groups based on consumption levels of carbohydrates, protein, and fat. Those with extremely low (<500 kcal) and high (>3500 kcal) energy intakes were excluded, as were those with a history of diabetes, cancer, or CVD.

Incident CHD was the outcome. Follow-up continued for 20 years. During follow-up, 1,994 participants developed CHD. Relative CHD risk comparing highest and lowest deciles of the low-carbohydrate diet score was 0.94 (95% CI, 0.74-1.19).

Author Thomas L Halton, ScD, Harvard School of Public Health, Boston, told GERIATRICS a low-carbohydrate diet may not provide better benefits than a low-fat diet in terms of CHD risk. "You can ... eliminate negative features of both diets by choosing healthy vegetable sources of fat and protein and working to reduce the glycemic load of the diet by substituting lower glycemic fruits, vegetables and whole grains, and vegetable sources of fat and protein for refined, high glycemic carbohydrates."

SOURCE: N Engl J Med. 2006; 355(19): 1991-2002

Guideline At-a-Glance

NAMS guidelines mark distinction between risk factors for osteoporosis and osteoporotic fracture

Source: Menopause 2006; 13(3):340-64.

Significant advancements in the management of osteoporosis have prompted new evidence-based guidelines from the North American Menopause Society (NAMS), Cleveland, Ohio.

The new guidelines, developed by a group of endocrinologists and gynecologists, are based on updated evidence from medical literature published since the 2002 version of the guidelines.

"One of the major differences [between these and the previous guidelines] is the recognition of the differences between risk factors for osteoporosis as defined by bone mineral density (BMD) and risk factors for osteoporotic fracture," Pam Boggs, NAMS Director of Education and Development told Geriatrics.

Osteoporosis is responsible for an estimated 90% of all hip and spine fractures in white American women aged 65 to 84. Authors identified reduction of fracture risk as the primary clinical goal of osteoporosis management. For BMD-defined osteoporosis, major risk factors in postmenopausal women are advanced age, genetics, lifestyle factors (ie, low calcium and vitamin D intake, smoking), thinness (body weight <127 pounds or body mass index <21 kg/m^2), and menopause status. Risk factors for osteoporotic fracture also include low BMD, previous fracture (other than skull, facial bone, ankle, finger, and toe) as an adult, and history of hip fracture in a parent. "For now, BMD is still the most reliable marker to predict fracture risk," said Boggs, who added that the World Health Organization is working on a better prediction method.

According to the guidelines, all postmenopausal women should undergo a history, physical examination, and any necessary tests to assess risk factors for osteoporosis and fracture. BMD testing is indicated only if the results will influence a treatment or management decision and is recommended for postmenopausal women with medical causes of bone loss, regardless of age, and postmenopausal women age ≥65, regardless of additional risk factors.

Lifestyle modifications that include a balanced diet, adequate calcium and vitamin D intake, appropriate exercise, avoidance of smoking and excessive alcohol use, and fall prevention are encouraged for all postmenopausal women. Boggs said the importance of vitamin D, in addition to calcium, plays a great role in osteoporosis management. The current National Academy of Sciences (NAS) RDA of vitamin D is 400 IU/d for women aged 51 to 70 and 600 IU/d for women age >70; NAMS recommends 700 to 800 IU/d for women at risk of deficiency. The NAS RDA of calcium is 1,000 mg/d for women aged 31 to 50 and 1,200 mg/d for women age ≥51.

Pharmacologic approaches to osteoporosis management are recommended for all postmenopausal women with:

- ► a history of osteoporotic vertebral fracture
- ► BMD values consistent with osteoporosis (ie, T-scores ≤-2.5)
- ► T-scores between -2.0 and -2.5 and one or more of the following: thinness, history of fragility fracture since menopause, or history of hip fracture in a parent.

Available pharmacologic options include bisphosphonates, selective estrogen receptor modulators (SERMs), parathyroid hormone, estrogens, and calcitonin. Studies have not compared these therapies for antifracture efficacy. Boggs said there is also a need for research on benefits of these drugs beyond 10 years.

Adherence is one of the major obstacles in osteoporosis management. Studies have shown adherence rates below 25% in as little as 6 months to 1 year. "One of the most important things doctors can do is encourage adherence, even if treatment consists of just lifestyle modification," said Boggs.

Take Home points

- New guidelines consider recognition of differences between risk factors for osteoporosis as defined by bone mineral density and by osteoporotic fracture
- Reduction of fracture risk is identified as a primary clinical goal of osteoporosis management
- For BMD-defined osteoporosis, major risk factors in postmenopausal women are advanced age, genetics, lifestyle factors, thinness, and menopause status
- Risk factors for osteoporotic fracture also include low BMD, previous fracture as an adult, and history of hip fracture in a parent

American Heart Association (AHA) Scientific Sessions, November 12-15, 2006, Chicago

Pharmacist intervention improves medication adherence in elderly

Pharmacist-directed education combined with prepackaging of medications increases compliance with medication schedules, leading to improvements in blood pressure and cholesterol levels among elderly patients, according to Allen J. Taylor, MD.

At the 2006 scientific sessions of the American Heart Association, he presented findings from the Federal Study of Adherence to Medications in the Elderly (FAME), which tested the effect of a comprehensive pharmacy program on medication adherence in 200 patients older than 65 (mean age: 78) who were taking four or more medicines daily. Baseline data were collected during a 2-month run-in phase, followed by an intervention phase during months 2 to 8. Following the intervention, 159 patients entered a randomized phase of continued pharmacy care versus return to usual care during months 8 to 14.

Patients in the study took an average of 9 chronic daily medications.

The pharmacy care program consisted of individualized medication education using standardized scripts, regular follow-up by pharmacists (every 2 months), and all medications dispensed in time-specified blister packs. During each individualized education session, patients were taught drug names, indications, strengths, adverse effects, and use instructions.

continued on pg. 17

Low testosterone increases CHD risk in older women

Low levels of testosterone are associated with an increased risk of mortality from coronary heart disease (CHD) in postmenopausal women, said Gail A. Laughlin, PhD, at the AHA scientific sessions.

Women's favorable cardiovascular risk compared with men is often explained by endogenous estrogen levels. However, few studies have evaluated the role of naturally circulating testosterone in older women. Hyperandrogenemia in young women with polycystic ovary syndrome is associated with adverse cardiovascular risk factors, carotid atherosclerosis, and impaired vascular function, said Dr. Laughlin, University of California, San Diego.

Using enrollees from the Rancho Bernardo Study, an ongoing population-based study of healthy aging in a southern California community, researchers assessed incidence of CHD events in 678 postmenopausal women aged 50 to 90 over a 20-year follow-up. None of the women were current estrogen users. Women were stratified into quintiles based on testosterone levels, with those in the lowest quintile having testosterone levels of 80 pg/mL or less.

"The normal testosterone level for women in this age group is around 170 pg/mL," she said.

Compared with women with higher levels of testosterone, women with testosterone levels in the lowest quintile had twice the risk of prevalent CHD, incident CHD (defined as a first ever MI or revascularization procedure), and CHD mortality. Further analysis showed that the association between low testosterone and increased cardiac risk was independent of the presence of CHD risk factors, diabetes, and the metabolic syndrome.

"This analysis was designed to answer the question of whether the association of low testosterone with mortality was specific to CHD or was related to other causes as well," said Dr. Laughlin, assistant adjunct professor of family and preventive medicine, University of California, San Diego. "We found that low low testosterone specifically predicted the risk of CHD death." It was not related to death from cancer or other causes.

Whether the results apply only to women who are not current users of estrogen awaits further study.

continued from pg. 16

After the intervention phase, medication adherence increased from 61.2% to 96.9%, systolic blood pressure declined from 133.2 mmHg to 129.9 mmHg (p=0.019), and low-density lipoprotein (LDL) cholesterol decreased from 91.7 mg/dL to 86.8 mg/dL (p=0.001).

After the randomized phase, there was sustained medication adherence in the continued pharmacy group (95.5%), whereas medication adherence fell to 69.1% in the group that reverted to usual care. "There was no durable effect of the program after having it withdrawn," said Dr. Taylor, chief of cardiology at Walter Reed Army Medical Center in Washington, DC. The improved persistence in the intervention group resulted in significant reductions in blood pressure compared with the usual care group (10.7 mmHg versus 3.1 mmHg; p=0.04), although the LDL cholesterol reduction during the intervention phase was sustained in patients later randomized to usual care.

The findings suggest that continued provision of blister-packed medications is a key component of a medication adherence program, given that the initial increase in medication adherence during 6 months of the pharmacy care adherence program did not persist in the patients who were randomized to usual care.

The medication prepackaging cost 14 cents per month, Dr. Taylor said, with the major expense of the program being the pharmacist's time, which may limit widespread use of the system. Nevertheless, Dr. Taylor said that a program to improve medication compliance may be warranted, considering the amount of money third-party payors and the Medicare system spend on the drugs.

"Because medication nonadherence is pervasive and morbid, the results of FAME call for greater emphasis within health care delivery systems and policy organizations on the development and promotion of clinical programs to enhance medication adherence, particularly among at-risk elderly," he said.

Fluvastatin XL/ezetimibe combo well tolerated in certain statin users

The combination of fluvastatin XL and ezetimibe effectively and safely lowers low-density lipoprotein (LDL) cholesterol in patients who previously experienced muscle-related side effects to other statins, said Evan Stein, MD, at the 2006 AHA scientific sessions in Chicago.

In a randomized, double-blind study, 85% of patients who had statin-associated muscle-related side effects had no muscle-related side effects when treated with either fluvastatin XL alone or in combination with ezetimibe, he said.

"Although rhabdomyolysis and myopathy are rare with statins, muscle-related side effects are a significant and growing problem," Dr. Stein said. In the PRIMO (Prediction of Muscular Risk in Observational conditions) survey of 7,924 patients in primary care practices who were receiving high-dose statin therapy, incidence of muscle-related side effects was 10.5%.

In the study presented here, 199 mostly high-risk patients who had a history of muscle-related side effects on statins were randomized to 12 weeks of treatment with fluvastatin XL, 80 mg/d, plus placebo; ezetimibe, 10 mg/d, plus placebo; or fluvastatin XL, 80 mg/d, plus ezetimibe, 10 mg/d. The average LDL cholesterol at baseline was approximately 175 mg/dL.

"As far as I know, this is the first study that recruited 100% of patients who had muscle-related side effects. Most of the patients had been on more than one statin," said Dr. Stein, from the Metabolic and Atherosclerosis Research Center in Cincinnati, Ohio.

The 12-week study duration was chosen because most of the patients in PRIMO who suffered muscle-related side effects to statin therapy did so within the first 3 months, he said.

Average reductions in LDL cholesterol were 15% with ezetimibe alone, 32% with fluvastatin XL alone, and 46% with the combination.

An LDL cholesterol <100 mg/dL was achieved by 10.6% of patients assigned to ezetimibe alone, 43.5% randomized to fluvastatin XL alone, and 73.4% randomized to the combination. For the optional LDL cholesterol goal of <70 mg/dL in high-risk patients, 40.5% achieved this goal on combination fluvastatin XL and ezetimibe, compared with only 9.1% on ezetimibe monotherapy and 18.5% on fluvastatin XL monotherapy.

"The combination is as good as the highest doses of simvastatin, atorvastatin, and moderate doses of rosuvastatin," Dr. Stein said. "We can have all of the guidelines and all of the drugs, but if patients can't take them, they're useless."

The incidence of muscle-related side effects was 24.2% with ezetimibe, 17.4% with fluvastatin XL, and 14.1% with the combination. Muscle-related side effects that led to discontinuation of the study drug occurred in 7.6% of ezetimibe patients, 4.3% of fluvastatin XL patients, and 3.1% on the combination.

Among the fluvastatin recipients, there were no additional patients who experienced muscle-related side effects after the first month of treatment, Dr. Stein said.

Long history of itchy red-brown papules

Condition persists year-round, but most common in summer

Norman Levine, MD

Minimally scaly reddish-brown reticulated papules coalescing into plaques, on the upper trunk and neck.

A 63-year old man presents with a longstanding history of a recurring, minimally pruritic eruption on the trunk and neck. It is most obvious in the summertime, but never disappears completely, even in the winter months.

On examination you observe numerous reddish-brown, minimally scaly, scalloped papules coalescing into plaques, over the upper trunk and neck area (figure).

Differential diagnosis

Consider conditions that produce scaly papules and plaques.

TINEA CORPORIS causes scaly red plaques that can occur on the trunk and neck. However, the lesions are normally annular, rather than being the confluence of many small scaly papules.

PSORIASIS can cause discreet and confluent scaly red papules and plaques. The scale is typically much thicker, and the lesions do not have a reddish-brown color. The lesions are often bright red.

SMALL PLAQUE PARAPSORIASIS produces small scaly reddish-brown papules, however, the lesions do not coalesce to the extent seen in this case.

TINEA VERSICOLOR is the correct diagnosis. This superficial fungal infection is caused by Malassezia furfur, a normal constituent of the host flora, which becomes pathogenic under conditions of heat and humidity. The lesions may vary in color from reddish-brown to almost white. The upper trunk and neck are common locations for this infection.

The patient was treated with ketoconazole, 400 mg, given in two doses over one week. The eruption resolved completely.

Diagnostic pearl

Tinea versicolor presents as reticulated scaly reddish-brown or hypopigmented papules that coalesce into plaques.

Dr. Levine is in private practice in Tucson, AZ.

Peripheral arterial disease

Management of peripheral arterial disease in the elderly

Wilbert S. Aronow, MD

Peripheral arterial disease (PAD) in the elderly can be: 1) asymptomatic, 2) associated with intermittent claudication, or 3) cause critical limb ischemia. Persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from coronary artery disease (CAD). Hypertension, diabetes mellitus, dyslipidemia, and hypothyroidism should be treated, and smoking should be stopped. Statins reduce the incidence of intermittent claudication and increase exercise duration until the onset of intermittent claudication in persons with PAD and hypercholesterolemia. Antiplatelet drugs (eg, aspirin, clopidogrel, angiotensin-converting enzyme [ACE] inhibitors, statins) should be given to all persons with PAD. Beta blockers should be given if CAD is present. Exercise rehabilitation programs and cilostazol lengthen exercise time until leg pain develops. Chelation therapy has no scientific basis and should be avoided. Revascularization or amputation may be indicated in some cases.

Aronow WS. Peripheral arterial disease. Management of peripheral arterial disease in the elderly. GERIATRICS 2007; 62(Jan):19–25.

Key words: peripheral arterial disease • intermittent claudication antiplatelet drugs • statins

Drugs discussed: aspirin • clopidogrel • ACE inhibitors • statins beta blockers • cilostazol

Peripheral arterial disease (PAD) is a chronic arterial occlusive disease of the lower extremities caused by atherosclerosis. PAD may cause intermittent claudication, ie, pain or weakness with walking that is relieved with rest. The muscle pain or weakness after exercise occurs distal to the arterial obstruction. Because the superficial femoral and popliteal arteries are most commonly affected by atherosclerosis, the pain of intermittent claudication is most commonly localized to the calf. Atherosclerotic obstruction of the distal aorta and its bifurcation into the two iliac arteries may cause pain in the buttocks, hips, thighs, or the inferior back muscles, as well as the calves.

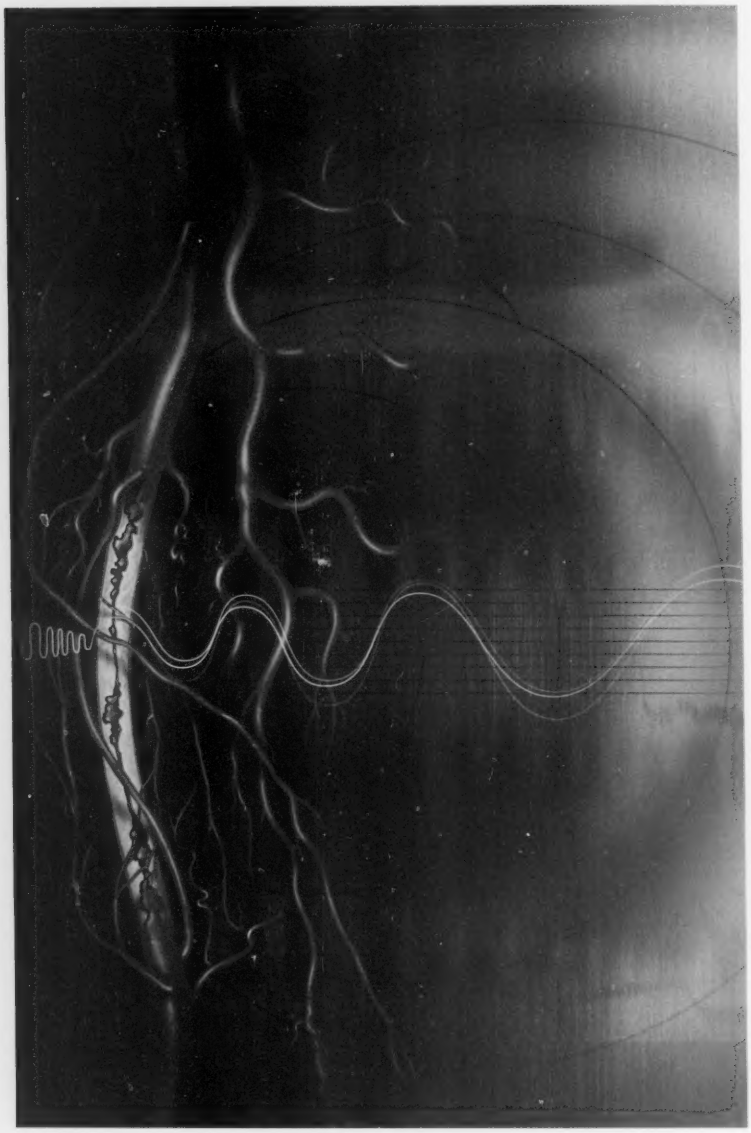
Dr. Aronow is clinical professor, Department of Medicine, Divisions of Cardiology, Geriatrics, and Pulmonary Medicine/Critical Care, New York Medical College, Valhalla, NY.

Disclosures: Dr. Aronow has no real or apparent conflicts of interest relating to the subject under discussion.

Upper extremity PAD will cause unequal blood pressure (BP) measurements in each arm. PAD patients also have a higher prevalence of cognitive impairment and erectile dysfunction.

Prevalence of PAD increases with age. In one study of 1,160 men (mean age: 80) and 2,464 women (mean age: 81), PAD was present in 32% of men and 26% of women ($p = 0.0001$).[1] Only one-half of elderly persons with PAD are symptomatic, a common presentation in the dysmobile frail elderly. Seniors with PAD may not walk far or fast enough to induce muscle ischemic symptoms because of comorbidities (eg, arthritis, pulmonary disease), may have atypical symptoms unrecognized as intermittent claudication, may fail to mention symptoms to their physician, or may have sufficient collateral arterial channels to tolerate arterial obstruction.

Women with PAD have a higher prevalence of leg pain on exertion and at rest, poorer functioning, and greater walking impairment from leg symptoms than men with PAD. Poorer leg strength in women contributes to poorer lower extremity functioning in women with PAD, compared with men. Modifiable risk factors that predispose to PAD include cigarette smoking, diabetes mellitus, hypertension, dyslipidemia, increased plasma homocysteine levels, and hypothyroidism.[2-5] PAD coexists with other atherosclerotic disor-



This illustration shows the arteries in the lower thigh with emphasis on the superficial femoral artery. The artery shows significant plaque and collateral supply. The collateral supply forms a 'cage' around the artery's disease portion. Overlaying the image is the Doppler effect. Between all these elements the illustration shows the disease pathology, and references clinical symptoms and test assessment.
Illustration for Geriatrics by Alexandra Baker

ders and with chronic kidney disease.[6,7] Persons with PAD are also at increased risk for all-cause mortality, and cardiovascular events and mortality.[8,9]

If arterial flow to the lower extremities cannot accommodate resting tissue metabolism, critical lower extremity ischemia occurs with pain at rest or tissue loss (necrosis of tissue). Critical ischemia causes rest pain in the toes or foot with progression to ulceration or gangrene. Chronic arterial insufficiency ulcers commonly develop at the ankle, heel, or leg. Mummified, dry, black toes or devitalized soft tissue covered by a crust is gangrene caused by ischemic infarction. Suppuration often develops with time, and dry gangrene changes to wet gangrene.[10]

Persons with lower extremity PAD have reduced or absent arterial pulses and may have bruits, muscle atrophy, hair loss, pallor/cyanosis, reduced skin temperature, and ulcers or gangrene.[10] Noninvasive tests to assess lower extremity arterial blood flow include measurement of ankle and brachial artery systolic blood pressures (SBP), characterization of velocity wave form, and duplex ultrasonography.

Measurement of ankle and brachial artery SBP using a Doppler stethoscope and BP cuffs allows calculation of the ankle-brachial index (ABI), which is normally 0.9 to 1.2. An ABI <0.90 is 95% sensitive and 99% specific for PAD diagnosis in older adults.[11] The lower the ABI, the more severe the restriction of arterial blood flow, and the more serious the ischemia. ABIs between 0.6 and 0.9 usually correlate with mild-to-moderate intermittent claudication. ABIs between 0.4 and 0.6 usually correlate with severe intermittent claudication. Rest pain and tissue loss often occur with ABIs between 0.25 and 0.4. Patients with calcified arteries from diabetes mellitus or renal failure occasionally have relatively non-compressible arteries leading to falsely elevated ABI values in the normal range. ABIs are measured using a Doppler stethoscope and BP cuffs. Doppler ultrasound tests are performed in a vascular laboratory.[37]

Correct use of medical therapy reduces excess mortality associated with PAD.[12-20] In addition, medical therapy may result in significant improvements in walking ability that may obviate the need for lower extremity angioplasty with stenting and bypass surgery.[10] Treatment of PAD is efficacious in older men and women.

Cessation of smoking

Current smoking significantly increases

PAD risk more than 2.6 times in elderly men and 4.6 times in elderly women.[2] Smoking increases amputation risk in persons with intermittent claudication. Patency in lower extremity bypass grafts is also worse in smokers than in nonsmokers. Smoking cessation reduces PAD progression to critical leg ischemia and reduces risk of MI and death from vascular causes. Cessation programs should be strongly encouraged in elderly persons with PAD. Smoking cessation is the most clinically and cost effective intervention for PAD treatment (table 1).

Table 1 Medical treatment of peripheral arterial disease

- ▶ Smoking cessation
- ▶ Treatment of hypertension: BP <140/90 mmHg and <130/80 mmHg in patients with diabetes mellitus or chronic renal disease
- ▶ Treatment of diabetes mellitus: Hemoglobin A1c level <7.0%
- ▶ Treatment of dyslipidemia: Serum low-density lipoprotein cholesterol level <70 mg/dl
- ▶ Use of antiplatelet drugs, clopidogrel or aspirin
- ▶ Use of angiotensin-converting enzyme inhibitors
- ▶ Use of beta blockers in patients with prior myocardial infarction or angina pectoris
- ▶ Use of statins
- ▶ Use of cilostazol
- ▶ Exercise rehabilitation

Source: Created for Geriatrics by WS Aronow, MD.

Treatment of hypertension

Hypertension significantly increased PAD risk 2.2 times in elderly men and 2.8 times in elderly women.[2] Hypertension should be adequately treated to reduce cardiovascular morbidity and mortality in persons with PAD (table 1). In the Heart Outcomes Prevention Evaluation (HOPE) Study (duration: 4.5 years), 1,715 persons (mean age: 67; range: age ≥ 55) had symptomatic PAD, and 2,118 had asymptomatic PAD with an ABI < 0.9.[12] In the HOPE Study, compared with placebo, ramipril, 10 mg/d, significantly decreased cardiovascular events by 25% in persons with symptomatic PAD; the drug also decreased symptoms.[12] Significantly, in this study, ramipril reduced absolute incidence of cardiovascular events by 5.9% in persons with asymptomatic PAD and by 2.3% in persons with normal ABI.[12] In the HOPE Study, the antihypertensive properties of ramipril did not completely account for the observed risk reduction.[12]

Among persons with PAD (mean age: 60) in the Appropriate Blood Pressure Control in Diabetes trial, lowering BP to a mean of 128/75 mmHg markedly reduced the number of cardiovascular events. Incidence of cardiovascular events in persons treated with antihypertensive drug therapy with enalapril or nisoldipine was 13.6% if the mean BP was decreased to 128/75 mmHg versus 38.7% if the persons received moderate antihypertensive drug therapy (mean BP: 137/81 mmHg; $p = 0.046$).[13] Although there is no evidence of improving PAD with control of hypertension and/or slowing its progression, ramipril has been reported to improve walking ability in patients with PAD.

Treatment of diabetes mellitus

Diabetes mellitus (types 1 and 2) significantly increased PAD risk 6.1 times in elderly men (mean age: 80) and 3.6 times in elderly women (mean age: 81).[2] Elderly persons with diabetes mellitus and PAD and no coronary artery disease (CAD) have a 1.5 times higher incidence of new coronary events than elderly nondiabetics with PAD and prior MI.[14] Diabetes mellitus should be treated with the hemoglobin A_{1c} level decreased to < 7% to decrease MI incidence.[21] BP should be reduced to < 130/80 mmHg in elderly persons with PAD and diabetes mellitus.[13,22] Elderly diabetics with PAD should also be treated with statins.[23]

Treatment of dyslipidemia

Dyslipidemia is a risk factor for PAD in elderly men and women.[2,3] Treatment of dyslipidemia with statins has been documented to reduce incidence of mortality, cardiovascular events, and stroke in elderly persons with PAD with and without CAD.[14-17] At 5-year follow-up of 4,444 men and women with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin significantly reduced incidence of intermittent claudication by 38%.[15] Three studies have also demonstrated that statins improve walking performance in persons with PAD.[24-26]

In a study of 264 men and 396 women, mean age 80 (range: 60 to 99 years), with symptomatic PAD and a serum low-density lipoprotein (LDL) cholesterol level ≥ 125 mg/dl, 318 of 660 persons (48%) were treated with a statin and 342 of 660 persons (52%) with no lipid-lowering drug.[17] At 39-month follow-up, statin treatment caused significant independent reduction (58%) in incidence of new coronary events, 52% reduction in persons with prior MI, and 59% in persons with no prior MI. Persons age > 80 had a similar reduction in incidence of new coronary events as those age < 80.

In the Heart Protection Study, 6,748 (33%) of 20,536 participants had PAD.[16]

Table 2 Efficacy of aspirin doses in reducing vascular death, nonfatal myocardial infarction, and nonfatal stroke in high-risk patients

Aspirin dose	Reduction in vascular death, myocardial infarction, or stroke
500-1500 mg (34 trials)	19%
160-325 mg (19 trials)	26%
75-150 mg (12 trials)	32%
<75 mg (3 trials)	13%

Source: Created for Geriatrics by WS Aronow, MD, with data from reference 21.

At 5-year follow-up, treatment with simvastatin, 40 mg/d, caused a significant 19% relative reduction and a 6.3% absolute reduction in major cardiovascular events independent of age, gender, or serum lipid levels.[16] These data favor statin therapy for elderly persons with PAD regardless of serum lipid levels.

Based on data, elderly persons with PAD should be treated with statins to reduce cardiovascular mortality and morbidity and PAD progression and to improve exercise time until intermittent claudication (table 1). PAD patients should have serum low-density lipoprotein cholesterol level reduced to < 70 mg/dL. No data show that reducing triglycerides reduces cardiovascular events in patients with PAD.

Treatment of increased plasma homocysteine

Increased plasma homocysteine level is a risk factor for PAD in elderly persons.[4] Lowering increased plasma homocysteine levels can be achieved by administering a combination of folic acid, vitamin B6, and vitamin B12. However, we do not have double-blind, randomized, placebo-controlled data showing that decreasing elevated plasma homocysteine levels will reduce coronary events and slow PAD progression in elderly persons with PAD.[27] One study by Lonn et al showed that lowering plasma homocysteine levels with folic acid and B vitamins in vascular disease did not reduce risk for the end point of MI, stroke, or death from cardiovascular causes, compared with placebo.[27] Another study by Bonaa et al showed in MI patients that lowering plasma homocysteine levels with folic acid and vitamin B12, with or without vitamin B6 did not reduce risk for the endpoint of MI, stroke, or death from coronary heart disease.[28]

Treatment of hypothyroidism

Hypothyroidism is a risk factor for PAD.[5] Elderly persons with clinical or subclinical hypothyroidism should be treated with l-thyroxine to reduce the CAD development and possibly PAD. However, no evidence shows that treatment with l-thyroxine will reduce PAD development or improve symptoms.

Antiplatelet drugs

Aspirin and clopidogrel are antiplatelet drugs used to decrease incidence of vascular death, nonfatal MI, and nonfatal stroke in persons with PAD (table 1).[18,19] Aspirin inhibits platelet aggregation by inhibiting the cyclo-oxygenase enzyme reaction within the platelet, blocking conversion of arachidonic acid to thromboxane A_2. Clopidogrel, a thienopyridine derivative, inhibits platelet aggregation by inhibiting binding of adenosine 5'-diphosphate to the platelet receptor.

The Antithrombotic Trialists' Collaboration Group(ATCG) reported a meta-analysis of 26 randomized studies of 6,263 persons with intermittent claudication due to PAD.[18] At follow-up, incidence of vascular death, nonfatal MI, and nonfatal stroke was 6.4% in patients randomized to antiplatelet drugs versus 7.9% in the controls, a significant reduction of 23% caused by antiplatelet therapy. The reductions are significant for all subgroups.

The ATCG also reported a meta-analysis of 12 randomized studies of 2,497 persons with PAD undergoing peripheral arterial grafting.[18] At follow-up, incidence of vascular death, nonfatal MI , and nonfatal stroke was 5.4% in persons randomized to antiplatelet drugs versus 6.5% in the control group, a significant reduction of 22% caused by antiplatelet therapy.

ATCG reported a meta-analysis of 4 randomized studies of 946 persons with PAD having peripheral angioplasty.[18] At follow-up, incidence of vascular death, nonfatal MI, and nonfatal stroke was 2.5% in patients randomized to antiplatelet drugs versus 3.6% in the control group, a significant reduction of 29% caused by antiplatelet therapy.[18]

Combining the 42 randomized studies of 9,706 persons with intermittent claudication, peripheral arterial grafting, or peripheral angioplasty, reveals incidence of vascular death, nonfatal MI, and nonfatal stroke at follow-up of 5.8% for persons randomized to antiplatelet drugs versus 7.1% for the controls, a significant relative risk reduction of 23% for antiplatelet therapy ($p = 0.004$), with similar benefits among persons with intermittent claudication, those with peripheral arterial grafting, and those with peripheral angioplasty.[18]

Aspirin

Table 2 shows the efficacy of different aspirin doses in reducing incidence of vascular death, nonfatal MI, and nonfatal stroke in high-risk persons.[18] Since aspirin doses > 150 mg/d do not reduce vascular death, nonfatal MI, and nonfatal stroke more than doses between 75 and 150 mg/d and cause more

gastrointestinal bleeding than lower doses, this author prefers an aspirin dose of 81 mg/d in treating the elderly with atherosclerotic vascular disease.

Clopidogrel

In the Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, 5,795 persons, mean age 64, with PAD were randomized to clopidogrel 75 mg/d and 5,797 persons, mean age 64, with PAD were randomized to aspirin, 325 mg/d.[29] At 1.9-year follow-up, annual incidence of vascular death, nonfatal MI, and nonfatal stroke was 3.7% in patients randomized to clopidogrel versus 4.9% in patients randomized to aspirin, a 24% significant relative risk reduction with use of clopidogrel ($p = 0.0028$).[29]

Based on the data, it is reasonable to conclude that clopidogrel is superior to aspirin in treatment of the elderly with PAD. Based on data, the author also recommends use of clopidogrel, 75 mg/d, in the treatment of elderly with PAD (table 1). However, clopidogrel costs more than aspirin. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend use of clopidogrel, 75 mg/d, as an effective alternative to aspirin, 75-325 mg/d, to reduce vascular death, MI, or stroke in persons with atherosclerotic lower extremity PAD.[19] The ACC/AHA guidelines also state that oral anticoagulant therapy with warfarin should not be given to lower risk of adverse cardiovascular ischemic events in those with atherosclerotic lower extremity PAD.[19]

ACE inhibitors

Data from the HOPE Study showed that ramipril, 10 mg/d, significantly decreased cardiovascular events in those with symptomatic PAD and in those with asymptomatic PAD.[12] Angiotensin-converting enzyme (ACE) inhibitors and statins also have many pleiotropic effects to account for their vascular protective properties beyond their primary mode of action, examples of which include inhibition of cellular proliferation, restoration of endothelial activity, inhibition of platelet reactivity, and an antioxidant potential.[30] ACC/AHA guidelines recommend treating persons with PAD with ACE inhibitors to reduce cardiovascular mortality and morbidity, unless there are contraindications to use of these drugs (table 1).[19] If the patient does not tolerate ACE inhibitors, then use angiotensin receptor blockers (ARBs).

Beta blockers

Elderly persons with PAD are at increased risk for developing cardiovascular events.[8] Many physicians have been reluctant to use beta blockers in persons with PAD because of concerns that beta blockers will aggravate intermittent claudication. However, a meta-analysis of 11 randomized controlled studies showed beta blockers do not adversely affect walking capacity or symptoms of intermittent claudication in persons with mild-to-moderate PAD.[31]

In an observational study of 575 men and women (mean age: 80) with symptomatic PAD and prior MI,[20] 85 persons (15%) had contraindications to beta blockers. Of the 490 persons without contraindications, 257 (52%) were treated with beta blockers. Adverse effects causing cessation of beta blockers occurred in 31 of the 257 persons (12%). At 32-month follow-up, beta blocker use caused a 53% significant independent reduction in incidence of new coronary events in elderly persons with PAD and prior MI.[20]

In a vascular surgery clinic, 301 of 364 persons (83%) with PAD and CAD were treated with beta blockers.[32] Beta blockers should be used to treat the elderly with PAD and prior MI or angina pectoris unless there are contraindications to use of these drugs (table 1).

Statins

Elderly persons with PAD and hypercholesterolemia should be treated with statins to reduce cardiovascular mortality and morbidity and PAD progression (table 1).[14-17] Based on data from the Heart Protection Study, persons with PAD should be treated with statins regardless of age, gender, or initial serum lipids levels.[16] ACC/AHA guidelines recommend treating patients with PAD with statins and to reduce the serum LDL cholesterol level to <70 mg/dl if they are at very high risk of ischemic events.[19]

Three double-blind, randomized, placebo-controlled studies have demonstrated that statins improve walking performance in persons with PAD.[24-26] In a study of 69 persons (mean age: 75) with intermittent claudication, a mean ABI of 0.63, and a serum LDL cholesterol level ≥ 125 mg/dl, 3 of 34 persons (9%) treated with simvastatin and 6 of 35 persons (17%) treated with placebo died before the 1-year study was completed.[24] Compared with placebo, simvastatin significantly increased treadmill exercise time until onset of intermittent claudication by 24% at 6 months and by 42% at 1 year after therapy (both $p < 0.0001$).[24]

In a study of 354 persons (mean age: 68), with intermittent claudication and hypercholesterolemia, at 1-year follow-up, compared with placebo, atorvastatin, 80 mg/d, significantly improved pain-free treadmill walking distance by 40% and significantly improved community-based physical activity.[25] In a study of 86 persons (mean age: 67), with intermittent claudication and hypercholesterolemia, at 6-month follow-up, compared with placebo, simvastatin, 40 mg/d significantly improved pain-free walking distance and total walking distance on a treadmill, significantly improved the mean ABI at rest and after exercise, and significantly improved symptoms of claudication.[26] Statin use is also associated with superior leg functioning independent of cholesterol levels and other potential confounders in patients with and without PAD.[33]

Treatment for walking distance

Many drugs have been shown to be ineffective in improving walking distance in persons with intermittent claudication.[34] Two drugs, pentoxifylline and cilostazol, have been FDA approved for symptomatic treatment of intermittent claudication. Chelation therapy should be avoided. Studies have demonstrated chelation therapy to be ineffective in PAD therapy.

Cilostazol

Cilostazol inhibits phosphodiesterase type 3, increasing intracellular concentration of cyclic adenosine monophosphate. Cilostazol suppresses platelet aggregation and also acts as a direct arterial vasodilator. Cilostazol has been demonstrated in numerous trials to improve exercise capacity in persons with intermittent claudication[35,36] and in a dose of 100 mg/bid, was shown to be superior to placebo and pentoxifylline.[36] After 24 weeks of treatment, there was a mean percent increase of 54% in mean maximal walking distance in the cilostazol group, versus a 30% mean percent increase in the pentoxifylline group ($p < 0.001$). Cilostazol has also been shown to cause a small increase in the ABI.[36]

However, cilostazol should not be administered to the elderly with PAD who also have heart failure. Other contraindications to use of cilostazol include a creatinine clearance <25 mL/min, a known predisposition to bleeding, or coadministration of CYP3A4 or CYP2C19 inhibitors (eg, cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole, HIV-1 protease inhibitors.)

Pentoxifylline

Pentoxifylline is a methylxanthine derivative that improves deformability of red and white cells. Many studies have found no consistent improvement with pentoxifylline in persons with intermittent claudication, compared with placebo.[36] The author's experience is that pentoxifylline causes a small effect on walking ability in older adults with intermittent claudication, and, therefore, prefers to use cilostazol to treat these persons (table 1). The ACC/AHA guidelines recommend using cilostazol in patients with lifestyle-limiting intermittent claudication in the absence of heart failure.[19] ACC/AHA guidelines also state that clinical effectiveness of pentoxifylline as therapy for intermittent claudication is marginal and not well established.[22]

Exercise rehabilitation

Exercise rehabilitation programs have been demonstrated to increase walking distance in persons with intermittent claudication via improvements in peripheral circulation, walking economy, and cardiopulmonary function.[37] The optimal exercise program for improving claudication pain distance in persons with PAD uses intermittent walking to near-maximal pain during a program of at least 6 months.[38] Strength training is less effective than treadmill walking and does not augment response to a walking exercise program whether used sequentially or concomitantly.[39] ACC/AHA guidelines recommend a supervised exercise program for patients with intermittent claudication (table 1).[19]

Foot care

Persons with PAD must wear properly fitted shoes. Careless nail clipping or injury from walking barefoot must be avoided. Feet should be washed daily and skin kept moist with topical emollients to prevent cracks and fissures, which may have portals for bacterial infection. Fungal foot infection must be treated. Socks should be wool or other thick fabrics, and padding or shoe inserts may be used to prevent pressure sores. When a foot wound develops, specialized foot gear (eg, casts, boots, ankle foot orthoses) may be helpful in unweighting the affected area.[10]

Angioplasty and bypass surgery

Indications for lower extremity percutaneous transluminal angioplasty or bypass surgery are 1) incapacitating claudication interfering with work or lifestyle, 2) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene, and 3) vasculogenic impotence.[19,40]

Amputation

Nonrandomized studies have demonstrated that immediate and long-term survival are higher in patients having revascularization rather than amputation for limb-threatening ischemia.[41] Amputation of lower extremities should be performed if tissue loss has progressed beyond salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations diminish the benefit of limb salvage.[10]

Conclusion

Only one-half of elderly adults with PAD are symptomatic. Individuals with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from CAD. Correct implementation of medical therapy reduces excess mortality associated with PAD, and may result in significant improvement in walking ability that may obviate a need for lower-extremity angioplasty with stenting and bypass surgery.

Clearly, treating older persons with PAD is efficacious. Medical treatment of PAD in the older patient includes, as applicable, smoking cessation, as well as treatment of hypertension, diabetes mellitus, and dyslipidemia. Drug therapy includes the antiplatelets, clopidogrel and aspirin, ACE inhibitors, beta blockers (in patients with previous MI or angina pectoris), statins, and cilostazol. Exercise rehabilitation is also helpful, and a program of supervised exercise training for patients with intermittent claudication is recommended by ACC/AHA guidelines. Finally, under certain circumstances, revascularization or amputation may be required.

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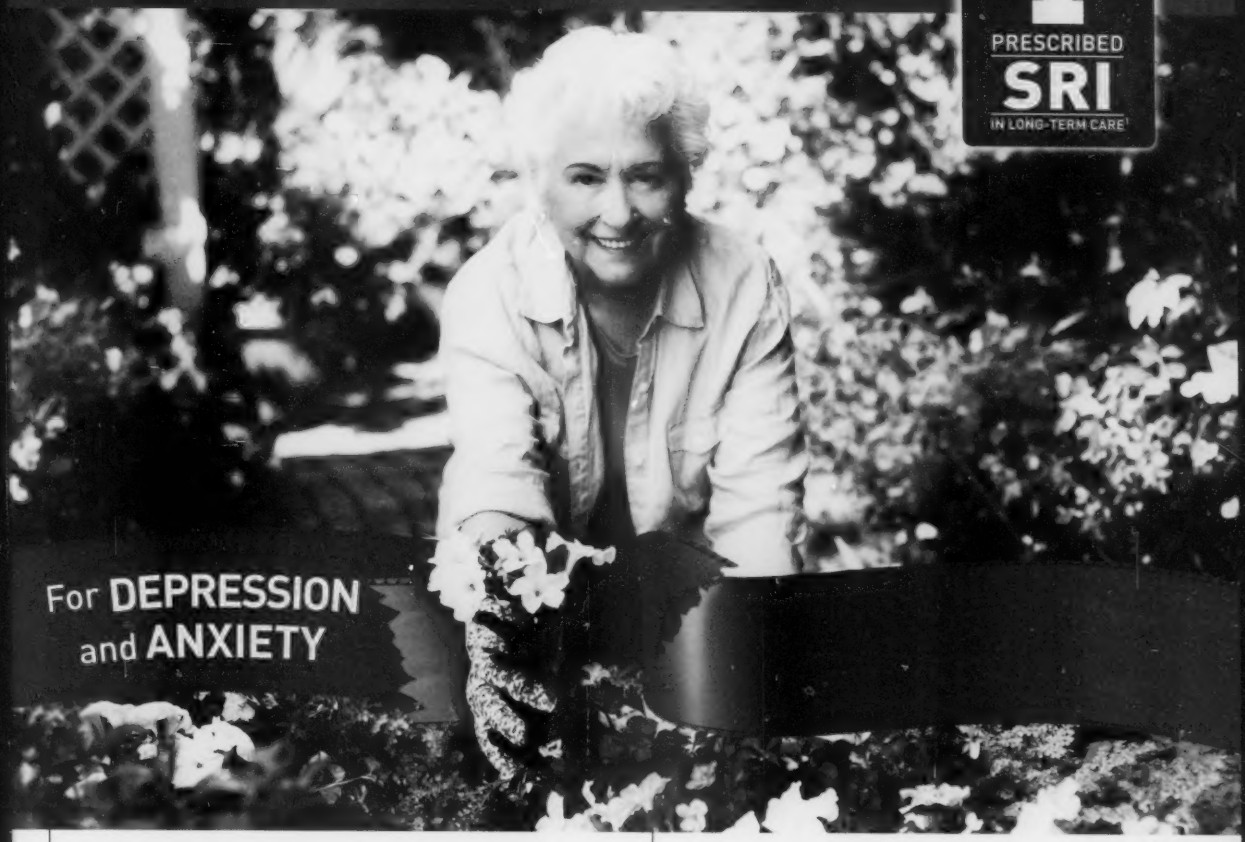

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Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), pimozide (see DRUG INTERACTIONS – Pimozide and Celexa), or in patients with hypersensitivity to escitalopram oxalate. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with Lexapro. As with other psychotropic drugs that interfere with serotonin reuptake, patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. The most common adverse events with Lexapro versus placebo (approximately 5% or greater and approximately 2x placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia.

References: 1. IMS National Prescription Audit. May 2005. **2.** Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry.* 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins;2003:552. **3.** LEXAPRO (package insert). St Louis, Mo: Forest Pharmaceuticals, Inc.; 2006. **4.** Greenblatt DJ, von Moltke LL, Hesse LM, Giancarlo GM, Harmatz JS, Shader RI. The S-enantiomer of citalopram: cytochromes P450 mediating metabolism and cytochrome inhibitory effects. Poster presented at: Annual Meeting of the Society of Biological Psychiatry; May 3-5, 2001; New Orleans, La.

Please see brief summary of prescribing information for LEXAPRO on following page.

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Brief Summary: For complete details, please see full prescribing information for Lexapro.

Suicidality in Children and Adolescents Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients (see Warnings and Precautions: Pediatric Use) Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**). Concomitant use in patients taking pimozide is contraindicated (see **Drug Interactions - Pimozide and Celexa**). Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Lexapro. **WARNINGS WARNINGS-Clinical Worsening and Suicide Risk Clinical Worsening and Suicide Risk** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase in almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there is substantial risk in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits. Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with Lexapro, in full prescribing information for a description of the risks of discontinuation of Lexapro**). **Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Lexapro is not approved for use in treating bipolar depression. **Potential for Interaction with Monoamine Oxidase Inhibitors In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome AND INCREASING DOSES** In two patients who were concomitantly receiving Lexapro and a triptan, a possible serotonin syndrome was observed. The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Lexapro treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS - Potential for Interaction with Monoamine Oxidase Inhibitors**). If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS - Drug Interactions**). The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS - Drug Interactions**). **PRECAUTIONS Information for Patients** Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Lexapro and triptans, tramadol or other serotonergic agents. **Drug Interactions Serotonergic Drugs** Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, St. John's Wort (see **WARNINGS - Serotonin Syndrome**). Concomitant use of Lexapro with other SSRIs, SNRIs or fluoxetine is not recommended (see **PRECAUTIONS - Drug Interactions**). *Triptans:* There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS - Serotonin Syndrome**). **General** Discontinuation of Treatment with Lexapro During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Abnormal Bleeding Published case reports have documented the occurrence of bleeding problems in patients treated with selective serotonin reuptake inhibitors. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. Hyponatremia Cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Lexapro treatment. All patients with these events have recovered with discontinuation of escitalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder. Activation of Mania/Hypomania In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. Interference with Cognitive and Motor Performance In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. Use in Patients with Concomitant Illness Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day (see **DOSAGE AND ADMINISTRATION**). Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate experience is gained, Lexapro should be used with extreme caution in patients with severe renal impairment (see **DOSAGE AND ADMINISTRATION**). Use in Patients with Concomitant Illness Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day (see **DOSAGE AND ADMINISTRATION**). Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate experience is gained, Lexapro should be used with extreme caution in patients with severe renal impairment (see **DOSAGE AND ADMINISTRATION** in full prescribing information). **Drug Interactions** CNS Drugs - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol - Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. Monoamine Oxidase Inhibitors (MAOIs) - See **CONTRAINDICATIONS** and **WARNINGS**. **Drugs That Interfere with Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with Lexapro. Cimetidine - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium - Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of lithium. However, lithium levels should be monitored in the appropriate adjustment to the dosage of lithium in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. Pimozide and Celexa - In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. Sumatriptan - There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. Theophylline - Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. Warfarin - Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine - Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough concentrations of carbamazepine were not affected, one case report suggests the possibility of carbamazepine toxicity upon addition of the two drugs together. Coadministration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. Ketoconazole - Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. Ritonavir - Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. CYP3A4 and -2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. Drugs Metabolized by Cytochrome P450 2D6 - *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers of debrisoquin (CYP2D6 deficient) and extensive metabolizers. In vivo coadministration studies of racemic citalopram with desipramine, a substrate of CYP2D6, also indicate a limited or absent effect of citalopram on CYP2D6. Cimetidine - Coadministration of cimetidine, a nonspecific inhibitor of cytochrome P450 enzymes, did not significantly affect the pharmacokinetics of escitalopram in a study investigating a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. Metoprolol - Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro and metoprolol had no clinically significant effects on blood pressure or heart rate. Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of ECT and escitalopram. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Racemic citalopram was administered in the diet to NMRI/BOM strain mice and CDBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown. Mutagenesis Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* human lymphocyte chromosomal aberration assay in the absence of metabolic activation. It was negative in the *in vivo* mouse micronucleus assay. Escitalopram was negative in the Ames test, in the *in vitro* mammalian cell gene mutation assay (HPRT locus), and in the *in vivo* mouse micronucleus assay. Impairment of Fertility In a fertility study in male and female rats, racemic citalopram, administered orally at doses of 5, 15, or 30 mg/kg/day, impaired male and female fertility at the highest dose tested, which is 3 times the maximum human dose on a mg/m² basis. Escitalopram was administered orally to male rats at doses of 5, 10, or 20 mg/kg/day, 7 days prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day. **Pregnancy Nonteratogenic Effects** Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**). Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. Currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery** The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers** Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother. In one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow-up information was available. The decision whether to breastfeed an infant during therapy with Lexapro should balance the potential benefits of breastfeeding for the infant and the potential risk of exposure to the infant to the drug. **PEDIATRIC USE** **WARNINGS** and **WARNINGS - Clinical Worsening and Suicide Risk**. One placebo-controlled trial in 264 pediatric patients with MDD has been conducted with Lexapro, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Lexapro in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use** Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{ss} was unchanged (see **CLINICAL PHARMACOLOGY**). 10 mg/day is the recommended dose for elderly patients (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse event information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment Major Depressive Disorder** Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder** Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. In the tables and tabulations that follow, MedDRA terminology has been used to classify reported adverse events. The incidence of side effects in patients treated with Lexapro in fixed-dose studies was generally similar to that seen in the flexible-dose range. Adverse events associated with discontinuation of drug were generally comparable in patients treated with Lexapro and those treated with placebo. Adverse events associated with discontinuation of drug in depressed patients treated with Lexapro were generally comparable to those seen in patients treated with other antidepressants. Approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see **TABLE 1**). **TABLE 1: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* (Lexapro (N=715) and Placebo (N=592)): Autonomic Nervous System Disorders:** Dry Mouth (6% and 5%), Sweating increased (5% and 2%) **Central & Peripheral Nervous System Disorders:** Dizziness (5% and 3%) **Gastrointestinal Disorders:** Nausea (15% and 7%), Diarrhea (8% and 5%), Constipation (3% and 1%), Indigestion (3% and 1%), Abdominal Pain (2% and 1%) **General:** Influenza-like Symptoms (5% and 4%), Fatigue (5% and 2%) **Psychiatric Disorders:** Insomnia (9% and 4%), Somnolence (6% and 2%), Appetite Decreased (3% and 1%), Libido Decreased (3% and 1%) **Respiratory System Disorders:** Rhinitis (5% and 4%), Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder* (9% and <1%), Impotence* (3% and <1%), Anorgasmia* (2% and <1%) *Events reported by at least 2% of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. †Denominator used was for females only (N=484 Lexapro, N=404 placebo). **Generalized Anxiety Disorder** Table 2 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder** Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. In the tables and tabulations that follow, MedDRA terminology has been used to classify reported adverse events. The incidence of side effects in patients treated with Lexapro in fixed-dose studies was generally similar to that seen in the flexible-dose range. Adverse events associated with discontinuation of drug were generally comparable in patients treated with Lexapro and those treated with placebo. Adverse events associated with discontinuation of drug in depressed patients treated with Lexapro were generally comparable to those seen in patients treated with other antidepressants. Approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see **TABLE 1**). **TABLE 1: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* (Lexapro (N=715) and Placebo (N=592)): Autonomic Nervous System Disorders:** Dry Mouth (6% and 5%), Sweating increased (5% and 2%) **Central & Peripheral Nervous System Disorders:** Dizziness (5% and 3%) **Gastrointestinal Disorders:** Nausea (15% and 7%), Diarrhea (8% and 5%), Constipation (3% and 1%), Indigestion (3% and 1%), Abdominal Pain (2% and 1%) **General:** Influenza-like Symptoms (5% and 4%), Fatigue (5% and 2%) **Psychiatric Disorders:** Insomnia (9% and 4%), Somnolence (6% and 2%), Appetite Decreased (3% and 1%), Libido Decreased (3% and 1%) **Respiratory System Disorders:** Rhinitis (5% and 4%), Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder* (9% and <1%), Impotence* (3% and <1%), Anorgasmia* (2% and <1%) *Events reported by at least 2% of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. †Denominator used was for females only (N=484 Lexapro, N=404 placebo). **Generalized Anxiety Disorder** Table 2 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder** Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of 1% or at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder** Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. In the tables and tabulations that follow, MedDRA terminology has been used to classify reported adverse events. The incidence of side effects in patients treated with Lexapro in fixed-dose studies was generally similar to that seen in the flexible-dose range. Adverse events associated with discontinuation of drug were generally comparable in patients treated with Lexapro and those treated with placebo. Adverse events associated with discontinuation of drug in depressed patients treated with Lexapro were generally comparable to those seen in patients treated with other antidepressants. Approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see **TABLE 1**). **TABLE 1: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* (Lexapro (N=715) and Placebo (N=592)): Autonomic Nervous System Disorders:** Dry Mouth (6% and 5%), Sweating increased (5% and 2%) **Central & Peripheral Nervous System Disorders:** Dizziness (5% and 3%) **Gastrointestinal Disorders:** Nausea (15% and 7%), Diarrhea (8% and 5%), Constipation (3% and 1%), Indigestion (3% and 1%), Abdominal Pain (2% and 1%) **General:** Influenza-like Symptoms (5% and 4%), Fatigue (5% and 2%) **Psychiatric Disorders:** Insomnia (9% and 4%), Somnolence (6% and 2%), Appetite Decreased (3% and 1%), Libido Decreased (3% and 1%) **Respiratory System Disorders:** Rhinitis (5% and 4%), Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder* (9% and <1%), Impotence* (3% and <1%), Anorgasmia* (2% and <1%) *Events reported by at least 2% of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. †Denominator used was for females only (N=484 Lexapro, N=404 placebo). **Generalized Anxiety Disorder** Table 2 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. 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Adverse events that were associated with the discontinuation of 1% or at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Generalized Anxiety Disorder* (Lexapro (N=429) and Placebo (N=427)): Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%), Sweating increased (4% and 1%) **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%), Paresthesia (2% and 1%) **Gastrointestinal Disorders:** Nausea (18% and 8%), Diarrhea (8% and 6%), Constipation (5% and 4%), Indigestion (3% and 2%), Vomiting (3% and 1%), Abdominal Pain (2% and 1%), Flatulence (2% and 1%), Toothache (2% and 0%) **General:** Fatigue (8% and 2%), Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%), Insomnia (12% and 6%), Libido Decreased (7% and 2%), Dreaming Abnormal (3% and 2%) Appetite Decre

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Meeting the mental health needs of older adults

Implications for primary care practice

Bradley E. Karlin, PhD • Jon D. Fuller, MD, AGSF

Greater attention to the mental health needs of older adults is critical in light of recent research documenting substantial undertreatment of mental health problems in late life. As often the first and only point of professional contact for mentally ill older adults, primary care physicians have an important and unique role in reducing enduring unmet mental health needs in late life. This article reviews the current state of geriatric mental health care delivery and provides valuable information and resources for use in clinical practice to increase and enhance primary care detection, treatment, and referral of psychological problems in older patients.

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Key words: geriatric mental health • primary care • screening • referral practice guidelines

Drugs discussed: psychotropic medications • atypical antipsychotics • zopiclone

Mental illness in late life is a serious public health concern. Aside from sizable emotional and social consequences, mental illness in late life leads to increased disability, poorer health outcomes, increased mortality risk, greater use of medical services, and reduced treatment compliance. Despite recent advances in mental health treatments for older adults (age 65 and older), less than one-third of older individuals with a mental health or substance use disorder receive treatment.[1,2] Compared with younger adults (age 18 to 64), older individuals are 3 times less likely to report receiving any form of outpatient mental health treatment.[2] Rates of mental health treatment among older adults are even lower in the specialty mental health care sector.[2,3]

When older individuals do seek treatment for mental health problems, they present to primary care physicians (PCPs) who often underdetect their psychopathology and attribute depression and other mental health problems to normal aspects of aging or medical disease.[4] Moreover, research examining physician prescribing and referral patterns has shown that when physicians do detect psychological problems in older adults, they heavily rely on pharmacotherapy and are much less likely to refer older patients for psychotherapy, compared with younger patients.[5] PCPs fail to detect and treat or refer 50% of patients with mental health problems, with an even greater number of mental health problems going undetected and untreated in older patients.[6]

In a recent study, physicians were found to assess for depression in only 14% of older patient visits; formal depression assessment tools were used in only 3 out of 389 patient visits.[4] Complicating detection of depression in primary care is the fact that somatic symptoms resemble symptomatology of medical illness or natural consequences of aging, and older patients are often unlikely to explicitly express a need for mental health treatment. Moreover, increased time constraints for PCPs can make detection of mental illness difficult to achieve.

Older adults often have limited knowledge of mental health and mental health services and, as a result, are

Dr. Karlin was affiliated with Psychology Service, VA Palo Alto Health Care System at the time this article was written. He is currently director, psychotherapy programs, at the Office of Mental Health Services, Department of Veterans Affairs, Washington, DC.

Dr. Fuller is deputy ACOS for geriatrics and extended care at VA Palo Alto Health Care System in California, and clinical assistant professor of medicine at Stanford University.

more likely than younger counterparts to rely on physicians as gatekeepers to the mental health care community. More than 80% of mental health care for depressed older individuals is provided in the primary care setting. When older adults do receive treatment in the primary care or mental health specialty sector, pharmacotherapy and psychotherapy often are below recommended guidelines.[7,8]

A review of health services research on quality improvement for depression in primary care concluded that "the outcome of major depression in the usual care of primary care is typically poor; this is particularly true of late life depression."[9] Limited attention to mental illness in geriatric primary care has led some to call for a transformation in the primary care model.[10]

Effectiveness of treatments

Evidence indicates older adults tend to respond as well as younger adults to psychotherapy and psychopharmacotherapy, though treatment often takes longer with older adults. Approximately 60% to 80% of depressed older adults recover from depression with treatment.[11]

Supported psychological interventions with older adults include cognitive-behavioral, interpersonal, and problem-solving therapies. When considering psychopharmacological treatments with older patients, careful attention to age-related changes in pharamacokinetics and dynamics of psychotropic agents is essential. Psychopharmacological and psychological interventions for late-life depression have been found to have similar efficacy.[12] Studies have shown an additive, non-duplicative benefit of combined treatment (pharmacotherapy + psychotherapy): patients, particularly more severely distressed patients, improve more from a combination of psychotherapy and pharmacotherapy than with medication alone.

Practice guidelines recommend combined treatment with more serious cases (eg, moderate to severe major depression) and when there is an identifiable psychosocial stressor.[13] Psychotherapy also often improves adherence to medication treatment and reduces premature termination.

Older adults appear to have more acceptance of mental health treatment compared with young adults

Recent national subjective outcome data indicate that older adults who receive mental health treatment typically report experiencing considerable benefit from the treatment, as much or greater than that reported by all other age groups.[2] Recent research has also shown greater acceptance of mental health treatment among cohorts of older adults.[14]

Depression has been studied most extensively, and evidence is growing for psychological treatments of other mental health problems, including anxiety disorders and mental health conditions and problem behaviors in dementia patients (eg, agitation, disruption, wandering).[15] This growing area of research has even greater significance because of recent widespread debate about whether psychotropic medications are effective or appropriate for managing neuropsychiatric symptoms associated with dementia. A recent JAMA review article concluded that "Pharmacological therapies are not particularly effective for management of neuropsychiatric symptoms of dementia."[16]

Evidence is growing about the positive effects of psychological interventions on late- life behaviors and cognitive functioning

Important safety concerns have been raised about use of atypical antipsychotic medications to treat neuropsychiatric symptoms of dementia. Last year, the FDA issued a public health advisory urging drug manufacturers to add warning labels to atypical antipsychotics due to an increased risk of mortality associated with use in dementia patients. A subsequent meta-analysis published in JAMA yielded similar results.[17] There is also evidence of increased risk of mortality among older adults treated with conventional antipsychotics. Exercise caution before prescribing antipsychotics to treat neuropsychiatric symptoms of dementia, especially to patients without comorbid psychosis. Physicians should give careful consideration to the risks and benefits and available alternative (eg, psychosocial) interventions.

Evidence is growing about the positive effects of psychological interventions on health-related behaviors and cognitive functioning in late life. For example, cognitive-behavioral therapy has been found to be superior to zopiclone for short and long-term management of insomnia in older adults.[18] In addition, cognitive retraining interventions often improve memory and other cognitive abilities in older adults.[19]

Consequences of late-life mental illness

Untreated mental illness in older

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THURSDAY APRIL 5	7:00 AM – 8:00 AM	*Registration and Breakfast in exhibit area*
	8:00 AM – 10:00 AM	**Prostate Cancer**
	10:30 AM – 12:30 PM	**Overactive Bladder**
	12:30 PM – 1:30 PM	***Single-sponsored CME Symposium***
		Lunch in exhibit area (boxed lunch)
	1:30 PM – 3:30 PM	**Benign Prostatic Hyperplasia**
	4:00 PM – 5:30 PM	**Surgery/Laparoscopy***
	5:30 PM – 6:30 PM	*Wine & Cheese Reception*
FRIDAY APRIL 6	7:00 AM – 8:00 AM	***Single-sponsored CME Symposium***
		Breakfast in exhibit area
	8:00 AM – 9:30 AM	**Hypogonadism**
	9:30 AM – 10:30 AM	**Infection**
	11:00 AM – 1:00 PM	**Renal Cell Cancer/Bladder Cancer**
	1:00 PM – 2:00 PM	***Single-sponsored CME Symposium***
		Lunch in exhibit area (boxed lunch)
	2:00 PM – 3:30 PM	**Kidney Stones**
	4:00 PM – 5:30 PM	**Sexual Dysfunction**
	5:30 PM – 6:30 PM	*Wine & Cheese Reception*
SATURDAY APRIL 7	7:00 AM – 8:00 AM	***Single-sponsored CME Symposium***
		Breakfast in exhibit area
	8:00 AM – 10:00 AM	**Surgery***
	10:30 AM – 12:30 PM	**Practice Management**
	12:30 PM – 1:30 PM	*Lunch in exhibit area (boxed lunch)*
	1:30 PM	**Conclusion**

*Additional fee applies

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Implement updated detection and diagnostic techniques for patients with urologic conditions
- Discuss the current treatment options for prostate cancer, renal cell cancer, and bladder cancer; OAB; renal calculi; sexual dysfunction; and BPH
- Identify emerging therapies for specific urologic disorders
- Learn about coding, reimbursement, and other practical nonclinical issues for managing your practice

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The sessions on hypogonadism are supported by an educational grant from Indevus Pharmaceuticals, Inc

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The sessions on overactive bladder are supported by an educational grant from Esprit Pharma, Inc

ESPRIT PHARMA

Table 1 Depression screening measures for older adults

No. items	Time	Cutoff	Other forms	Comments
Geriatric Depression Scale-SF (GDS-SF)[41]				
15	<5 min	5	GDS-5 (see below) GDS-LF (30 items)	Developed specifically for older adults and extensively studied (mainly outside of PC); exclude content assessing physical symptoms to avoid somatic bias; may be preferred with very frail patients; available in multiple languages
Geriatric Depression Scale-5 (GDS-5)[42]				
5	<2 min	2	GDS-SF (see above) GDS-LF (30 items)	Screener recently created from GDS-SF shown to perform well in limited research; a two-tiered approach has been suggested involving administration of the GDS-15 when cutoff is reached on GDS-5[43]
Patient Health Questionnaire-9 (PHQ-9)[44]				
9	<5 min	10	PHQ-2 (see below)	The newest of the depression screening measures developed specifically for PC; established ability to detect changes over time and therefore a good choice for monitoring treatment response; little research on use with older adults; operationalizes DSM-IV criteria, offering utility for diagnostic decisions
Patient Health Questionnaire-2 (PHQ-2)[45]				
2	<2 min	1	PHQ-9 (see above)	May be used as general initial screen (verbally or written) in busy clinics; follow-up positive response with PHQ-9 or other measure or clinical interview; little research on use with older adults; we do not recommend its use as sole choice with older patients, particularly those with multiple risk factors and more reserved patients
Beck Depression Inventory-PC (BDI-PC)[46]				
7	<5 min	4	BDI-II[47] (21 items)	Modified PC version of the well established BDI-II; less well studied with older PC patients, though available data indicate utility; not best choice for patients with physical morbidity
General Health Questionnaire-12 (GHQ-12)[48]				
12	<5 min	3/4		Validated in different ethnic groups, available in multiple languages; specificity somewhat limited in older PC patients
Center for Epidemiologic Studies-Depression Scale-10 (CES-D-10)[49]				
10	<5 min	4	CES-D-20[50] (20 items)	Shown to reliably assess for depressive symptoms but has not been validated against clinical diagnosis; greater empirical evidence for the original CES-D-20, which is available in multiple languages and validated for use with older ethnic minority groups; used primarily in research settings

Source: Created for Geriatrics by BE Karlin, PhD, and JD Fuller, MD, based on information from references 31, 41-52.

adults is associated with premature mortality to medical causes (due to new onset of medical conditions and exacerbation of existing illness) and suicide.[20,21] In a recent prospective study, the risk of developing any first cardiac event was twice as high for depressed than for nondepressed older adults (3 times as high for an ischemic event).[22] Several studies have also identified depression as an independent and major risk factor for death following MI.[23] In fact, depression has been found to be as much a risk factor for death as cardiovascular disease and diabetes among older primary care patients.[24] Furthermore, as many as 75% of older adults committing suicide have diagnosable depression.[25] Compared with younger patients, older adults who commit suicide are less likely to have received mental health specialty care and more likely to have seen a primary care provider shortly before committing suicide than are younger patients. In fact, up to 75% of older adults who completed suicide visited their primary care physician within a month of their suicide.[21] Yet a recent trial has shown that intervening in depression in elderly primary care patients significantly reduces the risk of suicide.[26]

Untreated mental illness in older adults is also associated with increased disability and dependence. Depression accelerates disability in dementia patients and leads to earlier nursing home placement.[27] In older adults with arthritis, treatment for depression has been found to decrease pain, improve functional status, and enhance quality of life.[28]

Untreated mental illness in older adults is also associated with substantial increase in medical service use, even after controlling for severity of chronic medical illness. Depressed older patients use a substantially greater number of medical services and have significantly higher health care costs than non-depressed older adults.[29] Mental illness in older adults also significantly increases risk of hospitalization by as much as 300%, and has been shown to increase patient use of nursing home staff time and costs.[30]

Table 2 Risk factors for late-life depression

Medical/physical
► Poor self-rated health
► Multiple comorbid physical illnesses
► Recent onset or worsening of medical illness
► Functional impairment
► Chronic pain
Psychological
► History of depression or other mental illness
► Limited interest in activities
► Sleep disturbance
Social
► Social isolation (especially if change from past)
► Withdrawal from friends or social activities
► Death of spouse or close loved one
► Widowed, divorced, or separated

Source: Created for Geriatrics by BE Karlin, PhD, and JD Fuller, MD.

Table 3 SIGECAPS: Mnemonic for assessing for diagnostic criteria of depression

- ► **S**leep disturbance (↑ or ↓)
- ► **I**nterest in previously enjoyable activities decreased
- ► **G**uilt, self blame, or worthlessness
- ► **E**nergy diminished
- ► **C**oncentration difficulties
- ► **A**ppetite disturbance (↑ or ↓)
- ► **P**sychomotor agitation or retardation (observable by others)
- ► **S**uicidal ideation

Major depressive disorder (MDD) = depressed mood or interest + 4 SIGECAPS for 2 or more weeks

Dysthymic disorder (DD) = depressed mood or interest + 3 SIGECAPS most days for 2 or more years

Depressive disorder NOS = fewer than the 5 items required for MDD for 2 or more weeks and does not meet criteria for DD

Source: Created for Geriatrics by BE Karlin, PhD, and JD Fuller, MD, based on information from references 22, 24.

Primary care screening, treatment, and referral

Improving detection of mental health problems in older patients can be achieved through use of efficient screening tools. Several depression

Table 4 Current practice guidelines for depression

Veterans Health Administration/Department of Defense[53]

Excellent set of guidelines for depression detection, treatment, and follow-up available for both primary care and specialty mental health care providers; includes interactive algorithms for different phases and useful pocket card; medication guidelines include specific prescribing guidelines for elderly patients

U.S. Preventive Services Task Force[51]

Provides good, concise review of the evidence for depression screening and treatment. The USPSTF is sponsored by the Agency for Healthcare Research and Quality and is the nation's leading independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services

Institute for Clinical Systems Improvement[54]

Thorough guidelines for assessment, treatment, and follow-up of depression in primary care; includes algorithms

Agency for Health Care Policy and Research Practice[55]

Reviews recent evidence for pharmacological and psychological treatment of depression in primary care; provides general, concise information to guide treatment in primary care

National Institutes of Health (NIH)[56]

Reviews the onset, course, treatment (psychotherapy and pharmacotherapy), and public health and related consequences of late life depression; developed by multidisciplinary team of NIH staff and experts

American Psychiatric Association[57]

Very detailed and informative set of guidelines for treatment of major depressive disorder in adults developed by psychiatrists; includes treatment considerations for older patients; provides among the most detailed information of existing guidelines; good desk reference

Expert Consensus Guidelines Series[13]

Detailed prescribing guidelines established by geriatric psychiatrists; available for purchase only

Source: Created for Geriatrics by BE Karlin, PhD, and JD Fuller, MD, based on references 13, 51, 53-57.

screening measures perform well from a psychometric and practical standpoint with older adults in primary care practice. Most depression screening measures are easily self-administered and can be completed in minutes in the waiting room. The U.S. Preventive Services Task Force currently recommends screening for depression in older and younger primary care patients. The benefit and feasibility of screening for depression in primary care has also prompted Medicare to include depression screening in the new preventive "Welcome to Medicare" exam for new beneficiaries. In November 2005, Aetna became the first national insurance program to increase reimbursement to primary care providers who actively screen for depression.

Table 1 compares depression screening measures that can be used with older primary care patients. Selection should be based on characteristics of the setting and the patient population. The screening measures include abbreviated versions of the Geriatric Depression Scale (GDS), the Patient Health Questionnaire (PHQ), the Beck Depression Inventory (BDI), the General Health Questionnaire (GHQ), and the Center for Epidemiologic Studies Depression Scale (CES-D). Especially busy clinics may prefer starting with brief screening measures (eg, PHQ-2; GDS-5), particularly with more healthy, active patients. A positive screen may be followed by administration of a more detailed screening tool (eg, PHQ-9, GDS-SF) or clinical interview.

When practically feasible, more detailed screening measures are recommended with older (65+) patients, particularly those with multiple risk factors or warning signs for depression (table 2).[31] Screening tools with similar cutoff scores across age groups (eg, PHQ) may be preferred in settings with a mix of older and younger patients. Clinics serving many older minority patients may use screening measures validated with different ethnic groups and available in multiple languages (eg, GDS, GHQ, CES-D).[31] Scales with little or no item content covering physical symptoms (eg, GDS; CES-D) may be most appropriate with very physically ill or disabled older patients. Exercise caution before using depression screening measures with cognitively-impaired patients because validity of screening measures is often limited with cognitively-impaired older adults.

Other measures exist for detecting depression in such patients, such as the clinician-administered Cornell Scale for Depression in Dementia[32] and Columbia Scale for Psychopathology in Alzheimer's Disease,[33] which are administered to caregivers.

If initial screening for depressive symptoms is positive or suggestive of a possible depressive disorder, a clinical interview to assess for DSM-IV criteria for depressive disorders is appro-

priate. SIGECAPS is a useful mnemonic for conducting the clinical interview (table 3). Re-administration of screening measures should be conducted at subsequent treatment visits. Among other warning signs, poor self-rated health status is a significant predictor of psychological distress in older and younger adults. This may be assessed with the question: "Overall, how would you rate your current health? Excellent, good, fair, or poor?" Knowledge of a patient's view of their health can provide insight into their psychological state and highlight particular cases (eg, responses of "fair" or "poor") where further screening or assessment may be warranted.

Because anxiety in older adults has been far less studied than depression, assessment instruments for anxiety in older adults are lacking, as are clinical guidelines for anxiety screening in older patients. The PHQ includes questions to assess for anxiety in primary care patients. The most common anxiety screening measure in mental health practice is the Beck Anxiety Inventory (BAI).

A primary care version of the BAI, the BAI-PC, was found to perform well in a small group of mixed-age primary care patients;[34] however, neither version has been empirically examined specifically with older primary care patients. Recently, a brief 7-item screening tool for assessing generalized anxiety disorder (GAD) was developed. The measure was found to be a valid and efficient method for screening for GAD in a mixed age sample.[35]

Even when depression and other mental health problems are recognized in older patients, there is often a failure to treat with medications or refer for specialized treatment.[36] Limited dissemination of practice guidelines (table 4) for treating depression in older patients has contributed to this problem, as has lack of awareness of specialized treatments and referral sources (table 5).

The next generation of treatment for depression in primary care are newly-developed collaborative care models in which a mental health specialist works in tandem with the primary care provider in the same clinic and provides consultation, psychoeducation, and, often, brief psychological treatment. Brief forms of psychotherapy, including problem solving therapy (PST–PC) and interpersonal therapy (IPT–PC), have been adapted for use in collaborative primary care programs.[31] Collaborative care models reduce physical and psychological barriers to mental health treatment, including enhancing the legitimacy and recognition of mental health issues and interventions among patients and professionals. Results from the recent Improving Mood-Promoting Access to Collaborative Treatment for Late-Life Depression (IMPACT) trial, which examined the effectiveness of such a coordinated care approach, found that coordinated care significantly increased treatment rates and doubled the effectiveness of usual care for depression among older primary care patients.[37] Information about the IMPACT model, including a toolkit and additional resources for incorporating the model into practice settings, can be accessed at: http://impact-uw.org/. Moreover, collaborative care for depression has been found to result in more sustained symptom improvement, and has been shown to be superior to consult-liaison models of care.[38] Relative to enhanced specialty referral models, integrated care approaches to depression in primary care have led to higher rates of treatment and greater treatment satisfaction among older adults.[39,40] Thus far, mental health screening and management approaches in primary care have focused almost exclusively on depression. It is important that future initiatives and research include screening and treatment for other forms of mental illness often undetected in older

Assessment instruments for anxiety **in older adults is lacking** as are clinical guidelines for anxiety screening

Table 5 Geriatric mental health specialist referral resources

Geropsychologists
National Register of Health Service Providers in Psychology https://www.nationalregister.com/osd/referral.php3 (select "Older Adults" in Search Criteria)
American Psychological Association (Find a Psychologist–all age groups) http://locator.apahelpcenter.org/
Geriatric psychiatrists
Geriatric Mental Health Foundation http://www.gmhfonline.org/gmhf/find.asp
Mental health services locator
Substance Abuse and Mental Health Services Administration (all age groups) http://www.mentalhealth.samhsa.gov/databases/default.asp

Source: Created for Geriatrics by BE Karlin, PhD, and JD Fuller, MD.

adults, such as anxiety and substance use disorders.

Conclusion

In short, greater attention to mental health problems among older adults in primary care is critically needed, especially given the role we now know that mental health problems has on physical health, service use, and longevity. Enhanced detection and treatment of mental health conditions in older primary care patients, including greater awareness of and referral to specialty mental health resources, can make substantial inroads to reducing enduring and substantial unmet mental health needs in late life and provide for more efficient and effective medical care and clinical outcomes.

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Outdated charts can lead to billing complications, jeopardized patient care

Don Self

Q.

How would you approach a fellow physician who does not keep his charts current? A colleague in my practice has charts scattered throughout his office. The charts date back to June 2006. I'm not sure why they are so behind, but he will not do anything to make them current. What would you recommend?

A.

If you and your office manager have not yet discussed this, I suggest you sit down with the doctor and find out why there is such a delay on the charts.

Because you did not elaborate, I do not know whether the charting delay is a time scheduling problem (he is scheduled to see too many patients), a procrastination issue or even a process issue (some physicians still mistakenly use a blank template and write SOAP on the side (a form of recording progress notes) and then fill in the documentation—despite the fact this does not meet the numerous CMS guidelines). It also may be possible that your doctor is not clear as to what has to be documented for each level of service or may wrongly assume that more documentation is needed than is required.

Point out the danger to his patients if the patient returns when the doctor is not there and another doctor has to treat the patient with only partial information. If your doctor puts patient care first, your discussion should have an impact. If the problem is timing or scheduling, then you need to make adjustments to how your staff is scheduling patients for this doctor. If the problem is the type of documentation, then you may want to look at simplifying the doctor's progress note by either using a template, electronic medical record, dictation, or some other method. If he believes that he's required to document a full page to support a level 3, 4 or 5 visit, then you may wish to review some of the coding techniques listed at http://www.donself.com.

If his delay is strictly procrastination, then note that you are not allowed to bill Medicare or Medicaid (or most carriers) until the documentation is completed, supporting the services being billed. Threaten to withhold billing until the paperwork is done. This is federal law and each person in the practice associated with filing a claim that is unsupported by documentation is equally liable if fraud charges are filed.

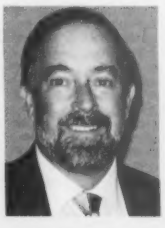
His tardiness in keeping his charts current can definitely impact you and the rest of the practice, as well as his ability to practice.

Q.

An older woman comes to my office to discuss a possible surgery. This patient says an orthopedic surgeon advised her that she needs a knee replacement. Since I am her internist, she wanted my advice. We discuss her options for 30 minutes. Would you code this as a office visit with a modifier 52, since an exam was not performed?

A.

No modifier is needed. If you spent more than half of the 30 minutes on counseling and/or coordination of care, you do not have to have an exam. Since you did not mention that the visit was requested by another health care professional, you cannot charge a consult, but you can definitely charge an office visit. Use the time shown in the CPT codebook to determine the level of office visit. Since you spent 30 minutes with the patient, you met or exceeded the 25-minute minimum for a 99214.



Don Self, an expert in Medicare coding, has been educating health professionals for 17 years. Send Medicare-related questions to Don Self c/o *Geriatrics*, 7500 Old Oak Blvd., Cleveland, OH 44130 (e-mail **donself@donself.com**). All questions will be answered; some will be published. No fee is charged for single questions; a consult fee may be charged for multiple questions. Access to related information is available on the web at: http://www.donself.com. The information in this column is designed to be authoritative. The publisher is not engaged in rendering medical or legal advice.

LIPITOR® (Atorvastatin Calcium) Tablets

Brief Summary of Prescribing Information

CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication. **Pregnancy and Lactation** — Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS: Liver Dysfunction — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal (ULN) occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS). **Skeletal Muscle — Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

PRECAUTIONS: General — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information). **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, *Skeletal Muscle*). ***Antacid:*** When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. ***Antipyrine:*** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. ***Colestipol:*** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. ***Cimetidine:*** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine. ***Digoxin:*** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. ***Erythromycin:*** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, *Skeletal Muscle*). ***Oral Contraceptives:*** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. ***Warfarin:*** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy — Pregnancy Category X: See CONTRAINDICATIONS.** Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. LIPITOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPITOR, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers** — Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use** — Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with LIPITOR had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls (see CLINICAL PHARMACOLOGY, *Clinical Studies* section in full prescribing information; ADVERSE REACTIONS, Pediatric Patients (ages 10-17 years); and DOSAGE AND ADMINISTRATION, *Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)* in full prescribing information. Adolescent females should be counseled on appropriate contraceptive methods while on LIPITOR therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). **LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.** Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients (see CLINICAL PHARMACOLOGY, *Clinical Studies: Homozygous Familial Hypercholesterolemia* in full prescribing information). **Geriatric Use** — The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 535 were elderly (≥65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group. The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

ADVERSE REACTIONS: LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences** — Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in the following table.

Adverse Events in Placebo-Controlled Studies (% of Patients)

BODY SYSTEM Adverse Event	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)—In ASCOT (see CLINICAL PHARMACOLOGY, *Clinical Studies* in full prescribing information) involving 10,305 participants treated with LIPITOR 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with LIPITOR was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)—In CARDS (see CLINICAL PHARMACOLOGY, *Clinical Studies* in full prescribing information) involving 2838 subjects with type 2 diabetes treated with LIPITOR 10 mg daily (n=1428) or placebo (n=1410), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: *Chest pain*, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. ***Digestive System:*** *Nausea*, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. ***Respiratory System:*** *Bronchitis, rhinitis*, pneumonia, dyspnea, asthma, epistaxis. ***Nervous System:*** *Insomnia, dizziness*, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia. ***Musculoskeletal System:*** *Arthritis*, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. ***Skin and Appendages:*** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. ***Urogenital System:*** *Urinary tract infection, hematuria, albuminuria*, urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. ***Special Senses:*** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. ***Cardiovascular System:*** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. ***Metabolic and Nutritional Disorders:*** *Peripheral edema*, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. ***Hemic and Lymphatic System:*** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia. **Postintroduction Reports** — Adverse events associated with LIPITOR therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, and fatigue. **Pediatric Patients (ages 10-17 years)** In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of LIPITOR 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY, *Clinical Studies* section in full prescribing information and PRECAUTIONS, *Pediatric Use*).

OVERDOSAGE: There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Please see full prescribing information for additional information about LIPITOR.

℞ only

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More than powerful reductions in LDL-C

Powerful reductions in events

Proof that LIPITOR helps both moderate-risk and high-risk†‡ patients*

Nonfatal MI[1]

45%

relative risk reduction seen in **ASCOT-LLA**[1] (P=.0002)

Stroke[1]

48%

relative risk reduction seen in **CARDS** (P=.016)

*ASCOT-LLA assessed the effect of LIPITOR 10 mg vs placebo on fatal and nonfatal CHD in 10,305 treated hypertensive patients without previous MI and with TC ≤251 mg/dL. All patients had ≥3 CV risk factors such as age ≥55 years, smoking, low HDL-C, or family history of CHD. The primary end point demonstrated a 36% relative risk reduction of nonfatal MI and fatal CHD (P=.0005).[2]

†CARDS included 2838 patients aged 40 to 75 years with type 2 diabetes, LDL-C ≤160 mg/dL, TG ≤600 mg/dL, and no history of CHD, stroke, or other major CV events, and a documented history of ≥1 additional risk factor including retinopathy, albuminuria, hypertension, or current smoking. Patients were randomized to either LIPITOR 10 mg (n=1428) or placebo (n=1410). The primary end point demonstrated a 37% relative risk reduction of major CV events (P=.001).[3]

‡Patients in CARDS had type 2 diabetes, which is considered a CHD risk equivalent according to the NCEP ATP III guidelines.[4]

RESULTS TO TRUST.
BENEFITS TO LOVE.

LIPITOR®
atorvastatin calcium
tablets

LIPITOR is indicated to reduce the risk of myocardial infarction, revascularization procedures, angina, and stroke in adult patients with multiple risk factors but without clinically evident CHD; to reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes and without clinically evident CHD, but with multiple risk factors; as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels; and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

LIPITOR is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women who are or may become pregnant or who are nursing; in patients with hypersensitivity to any component of this medication.

Rare cases of rhabdomyolysis have been reported with LIPITOR and other statins. With any statin, tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected, if creatine phosphokinase (CPK) levels rise markedly, or if the patient has risk factors for rhabdomyolysis.

Due to increased risk of myopathy seen with LIPITOR and other statins, physicians should carefully consider combined therapy with fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or niacin and carefully monitor patients for signs or symptoms of myopathy early during therapy and when titrating dose of either drug.

It is recommended that liver function tests be performed prior to and 12 weeks following both the initiation of therapy and any elevation of dose, and periodically thereafter. If ALT or AST values >3 x ULN persist, dose reduction or withdrawal is recommended.

In clinical trials, the most common adverse events were constipation, flatulence, dyspepsia, and abdominal pain.

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** Sever PS, Dahlöf B, Poulter NR, et al, for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-1158. **3.** Colhoun HM, Betteridge DJ, Durrington PN, et al, on behalf of the CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696. **4.** Grundy SM, Cleeman JI, Bairey Merz CN, et al, for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.

Please see brief summary of prescribing information on adjacent page.

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